VOL. 37 APRIL 1961 NO. 4

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Article by

L. E. BURNEY

ANNUAL MEETING ADDRESSES

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Transcription of a Panel Meeting on Therapeutics

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REFERENCES: 1. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 2. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1950. 3. Wainer, A. S.: Ann. New York Acad. Sc. *86*:250, 1960. 4. Clinical data in files of the Medical Department, Irwin, Neisler & Co., 1959, 1960. 5. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 6. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 7. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 8. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960.

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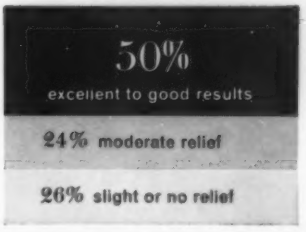
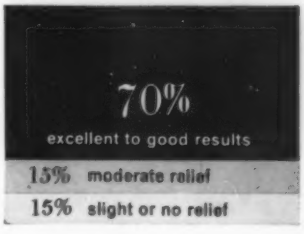
"...predictability of satisfactory control of a painful state is high..."[1]

low back pain



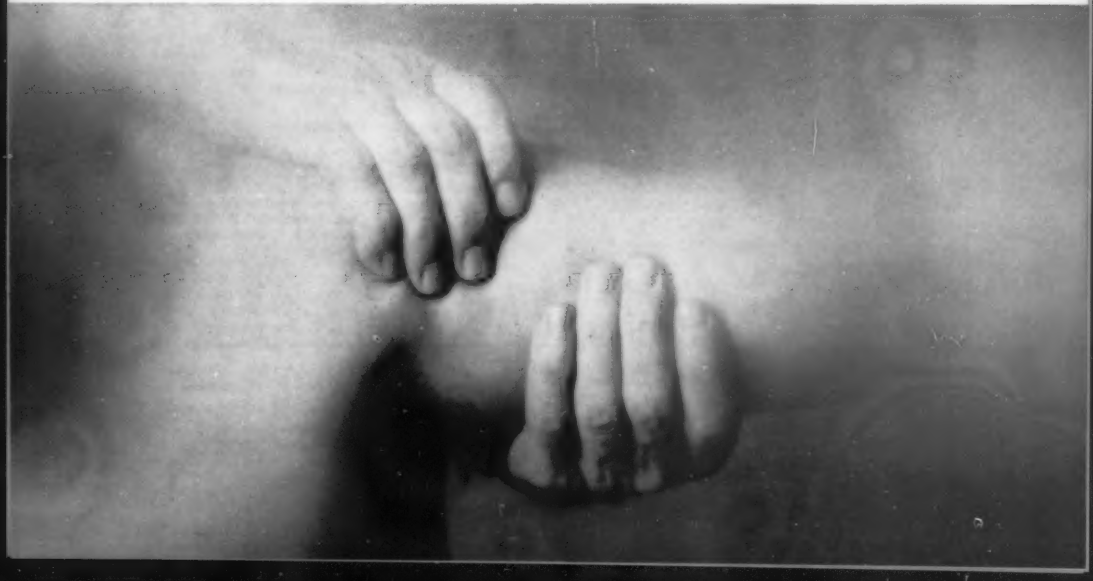
musculoskeletal pain*



*Including muscle strains and tears, arthralgia, muscular rheumatism and spasm.

raises pain threshold

relaxes muscle tension



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REFERENCES:

1. Scherbel, A. L.; Schuchter, S. L., and Harrison, J. W.: Cleveland Clin. Quart. 24:98, April, 1957.
2. Waine, Hans: Arthritis, rheumatoid, in Conn, H. F.: Current Therapy 1959, Philadelphia, W. B. Saunders Co., 1959, p. 565.

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PACKAGE INFORMATION: ELASE is supplied as an ointment in 30-Gm. and 10-Gm. tubes. Disposable vaginal applicators (V-Applicators) for application of ointment are available separately in packages of 6. ELASE is also supplied as lyophilized powder in rubber-diaphragm-capped vials. To be maximally effective, the solution must be freshly reconstituted with isotonic sodium chloride just prior to topical use. Within six hours after preparation, half of its potency is lost at room temperature.

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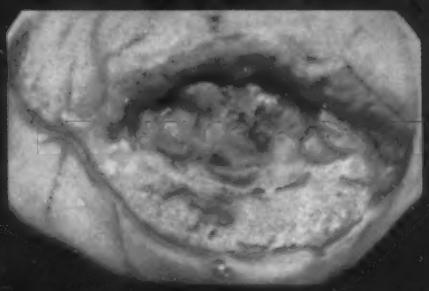
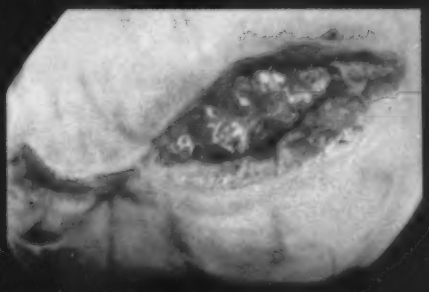


Draining wound four weeks postoperatively and prior to enzymatic therapy. Infective organisms identified were Pseudomonas and coagulase-positive staphylococci.



Eight days later. Solution containing 50 Loomis units fibrinolysin and 50,000 units desoxyribonuclease applied topically, for periods of three hours 3 times daily, for seven days. Considerable improvement in fibrinopurulent base of stump.

REFERENCES: (1) Coon, W. W.; Wolfman, E. F., Jr.; Foote, J. A., & Hodgson, P. E.: Am. J. Surg. *98:1, 1959. (2) Friedman, E. A.; Little, W. A., & Sachtleben, M. R.:* Am. J. Obst. & Gynec. *79:474, 1960. (3) Margulis, R. R., & Brush, B. E.:* Arch. Surg. *65:511, 1952. (4) Personal Communications to the Department of Clinical Investigation, Parke, Davis & Company, 1959.*

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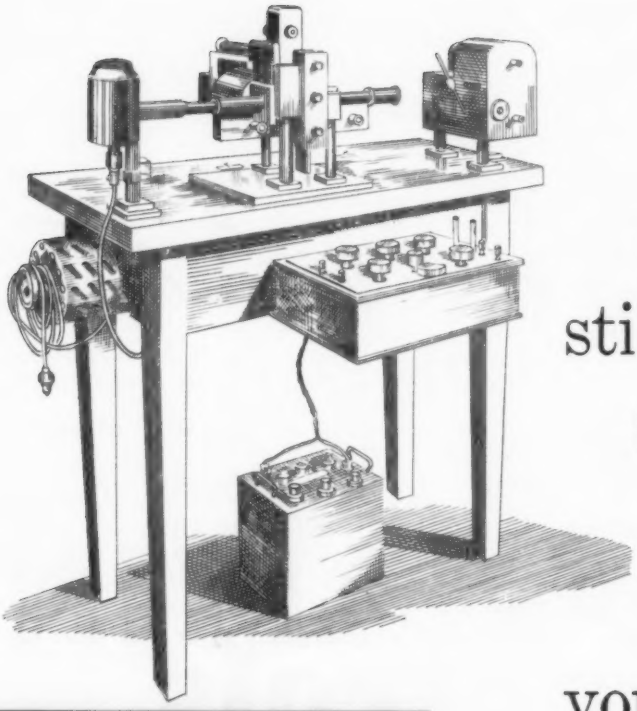

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 37, NO. 4 APRIL 1961

THE FUTURE OF THE ACADEMY

*Address of the Retiring President**

ROBERT L. LEVY

HAPPILY, both for you and for me, a detailed account of the Academy's activities during the past year will not be presented at this time. A report of happenings during 1958 and 1959 has been printed and circulated, and it is planned to issue a similar pamphlet biennially. Certain projects, recently initiated, will be referred to in brief, largely because it is in the future that they will come to full fruition.

In association with five of the medical colleges in the metropolitan area, and the Rockefeller and Sloan-Kettering Institutes, a Medical Library Center is being planned. Its location is still undetermined. Here will be deposited, and made readily available, the little-used material which crowds the shelves of every active library. Funds for the project are being collected and already, in this respect, there has been a considerable measure of success, due to the generous support of several foundations. A Board of Trustees, composed of the deans of the Medical Schools concerned, as well as representatives of the two Institutes and of the Academy, is presently functioning. A librarian has been

* Delivered at the Annual Meeting of The New York Academy of Medicine, January 5, 1961.

chosen and will assume preliminary duties early this year. This undertaking, though not novel in its conception, has far-reaching implications, both from the point of view of added space for the participating libraries and of better facilities for research workers in medicine and allied sciences.

Another innovation has been the establishment of a Clinical Science Course, designed particularly for recent graduates at resident level but available, also, as a review program for physicians at all levels of training and practice. The aim is to present the basic sciences in their relation to clinical medicine. The response, as evidenced by a large attendance, has been gratifying. Apparently, a need in the field of graduate medical education has been met, at least in part.

In response to a petition, signed by twenty Fellows, the Trustees and Council, at their last meeting, recommended the formation of a Section on Occupational Medicine. To-night, you have voted favorably on this proposal. This field of medicine is of growing importance, for it involves large groups of workers in industry. The physicians who serve the employer corporations aim to place these persons in proper jobs, with regard to physical capabilities and handicaps, to prevent disease and to recognize it in its incipiency. By so doing, they make a material saving in manpower and effective working hours. Furthermore, there is opportunity, in this area of medical practice, for clinical investigation, which may well yield results of wide general interest.

In August, 1960, Mr. Robert Moses, President of the New York World's Fair, which is to be held in 1964 and 1965, asked, by letter, whether the Academy would sponsor, and aid in organizing, a Health and Medicine Exhibit. After further written communications and several meetings with the Vice-President in charge of this division, the matter was presented to the Trustees and Council at their November meeting. Approval was voted and Mr. Moses was so informed. On December 9, he wrote, laconically: "Thanks loads for your letter about the Hall of Man, Health and Medicine Exhibit. I begin to see daylight". The necessary steps for action are being taken.

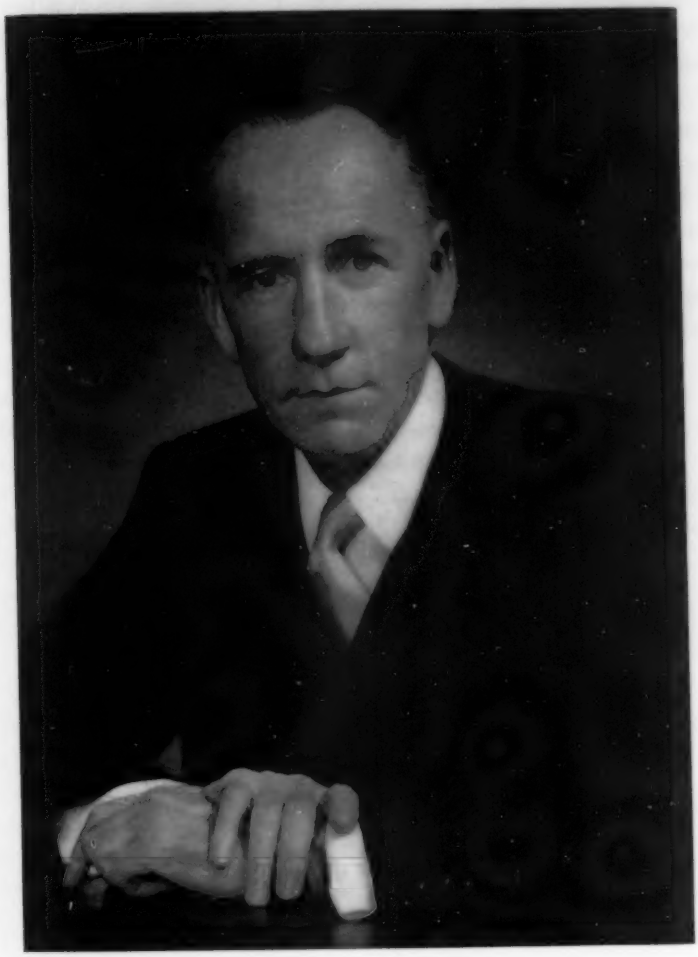
Without using a crystal ball, here is a quick look into the future. There is a real place for the Academy in the years to come. But, if it is to continue having an influence not only locally, but nationally and internationally as well, its viewpoint must be adapted to the rapidly changing scene, as occasion may demand. Medicine embraces many new

and expanding disciplines which call for modification in educational approach. Its social and economic aspects assume growing importance as government plays an ever-increasing role in its support and development. It is the duty of physicians, both as individuals and as groups, to participate actively in the effort to promote policies that are sound and honest. This Academy can, and will, without doubt, play its part.

To enter a wider arena and meet rising costs, additional monies are required. Accordingly, a Committee on Public Relations and Financial Development has been appointed and is at work.

For me, these past four years as President, have been stimulating and educational. It has been possible to work closely with an able, full-time staff and with many Fellows of the Academy who have given freely of their time and abilities to serve on various committees. I have enjoyed, especially, an intimate association with Dr. Howard Craig, who has acted as mentor and guide. He is, in every sense, the Director.

It now gives me pleasure to present the new President. He is the distinguished Stimson Professor of Surgery at Cornell University Medical College and Surgeon-in-Chief to The New York Hospital – Dr. Frank Glenn.



FRANK GLENN, M.D.

MEDICINE'S INCREASING RESPONSIBILITIES

*Inaugural Address**

FRANK GLENN

President, The New York Academy of Medicine

You confer upon me great honor in selecting me as your president. You have my sincere appreciation and a solemn pledge to serve you to the best of my ability. As I recall those who have preceded me and what they have accomplished, I feel some trepidation and I am both humble and proud. Dr. Robert Levy has spoken to you about the splendid record of achievement during his term of office. With the able assistance of the director, Dr. Howard Craig, and the Council—which includes Dr. Levy—I look forward to a vigorous pursuit of the Academy's goals.

Since it was established, 114 years ago, the illustrious New York Academy of Medicine[1] has served well the medical profession and the people—not only of the five boroughs of the City of New York—but also of our state, our nation and many countries throughout the world. The scope that medicine encompassed one hundred years ago was far more limited than it is today. During the first fifty years of the past century, developments in our profession seemed to move slowly, but in the five decades just passed, they have advanced with ever increasing rapidity. The outposts of medicine have pushed forward like the pseudopods of a huge and growing amoeba as seen under a microscope. New fields have opened up, have flourished, and have given rise to still newer frontiers; and the trend continues at an increasing pace.

This evolutionary process has tremendously enlarged the capacity of modern medicine to minister to man, thus placing a growing burden of responsibility upon the medical profession. It is my objective here to indicate the significance and magnitude of these responsibilities. For

* Delivered at the Annual Meeting of The New York Academy of Medicine, January 5, 1961.

purposes of discussion, we may list them under four headings: 1) Scientific, 2) Sociologic, 3) Economic, and 4) Political.

Scientific: Advances in the basic sciences through research have ever been the paving blocks for the highway of medical progress. Mention of only a few contributions of the basic sciences will illustrate their far-reaching effect on patient care. The development of the roentgen ray, the creation of immunity against bacterial and viral diseases, the chemical synthesis of bactericidal drugs, the tagging of organic compounds with radioactive substances, and such discoveries as the anesthetic effect of sulfuric ether, penicillin and other antibiotics and most recently, "acquired immunologic tolerance"[2] that promises to make organ transplantation feasible and practical, all have actually contributed or are likely to contribute to the prevention and cure of human disease, the relief of suffering, and the prolongation of life.

Such discoveries are being adopted into the complex field of clinical medicine with far less delay than they were in the past. They are reflected in reduction of infant mortality rates, control of infectious diseases, and greater safety and ease with which both diagnostic and therapeutic surgical procedures are now accomplished. The Academy has always participated in expediting this flow of scientific advances from wherever they may originate into clinical medicine where they can achieve their ultimate human good, the improvement of patient care. The fact that the facilitation of this transfer was recognized as a primary objective by our predecessors, the founders, is evidenced by our library and our committees on medical education and public health. To meet the health problems of this huge urban area of eight million people,[3] the talents and resources of institutions like this Academy are much needed. Furthermore, and indirectly, whenever such an institution successfully recognizes and solves a problem that is common to other large cities, it sets an example that may have far-reaching and beneficial influence.

Sociologic: Since 1900 the population of this country has more than doubled.[4] The present rate of increase is so dramatic that it is referred to as being explosive. Contributing to our growth in numbers is increased survival of the newborn and infants, better control of disease, and improved living conditions. These and other factors have increased the average life span to 70 years from less than 50 years a half century ago.[5]

A majority of our people now live in cities and large towns, whereas formerly they were located in rural areas and villages. In this period, also, machines have come to do much of man's work. Labor organizations now forecast a three to four day work week. Urban living in this machine age tends to deprive children of the discipline of doing household chores or even walking short distances. Retirement at 60 or 65, while life expectancy is extended, increases the total leisure of all. The medical profession must participate in solving some of the problems that are bound to arise along with these benefits: how to pursue a long life to its complete fulfillment; how to avoid delinquency in our children; how to prevent unbecoming indulgences amongst our adults; and how to protect the aged from feeling unwanted.

Our Fellows represent a great composite of medical talent from private practice, medical schools, research organizations, hospitals, government agencies, and insurance groups. This wealth of ability should be utilized in seeking solutions to these current complex social problems, for while they have many nonmedical facets, the medical profession probably has a better understanding of them than any other single group.

Economic: An indication of the magnitude of expansion in medicine over the past century is to be found in the development of hospitals during that period. One hundred years ago there were only a few relatively simple institutions, and these were devoted primarily to custodial care, and located in the larger cities. Now our hospitals are complex organizations, providing for a multitude of functions and so numerous that only a few communities are remote from them. To operate them requires highly trained personnel, ample facilities, varied equipment, and expensive and perishable supplies. The cost of this aggregate is great—so great that the average citizen cannot afford to pay for his share when he becomes a patient.

The teaching institutions, medical schools, nursing schools, and hospitals which provide instruction and training of personnel, must struggle to make ends meet. Interne and resident training programs impose even greater financial burdens upon those who conduct them. At present, there is considerable controversy over insurance coverage and the diversion of service patients formerly involved in teaching to a private patient category, thus crippling many teaching programs. The

solution of this problem is urgent, because future health needs of the nation demand efficient teaching programs now.

Inherent and inseparable in teaching institutions is research, so essential to improvement and future advancement. This, too, is costly. As advances in knowledge and technology take place, facilities and equipment soon become obsolete. Likewise, costly supplies to meet the daily requirements of patient care and the inflationary trend in our economy burden our teaching hospitals with an estimated 6 to 7 per cent annual increase[6] in their budgets.

A just distribution of the costs of medical care may be anticipated only when both the profession and the lay citizenry are correctly informed and can view the overall problems in proper perspective. The unique position of The New York Academy of Medicine in relationship to other local medical organizations and institutions should enable it to help accomplish this end.

Political: The scientific, sociologic, and economic aspects of medicine clearly indicate why medicine's responsibilities are rapidly increasing and, to some extent, why certain of these require urgent consideration. The solution to many difficulties in various areas of endeavor throughout the United States is being sought by increasing government participation. This has been particularly true for matters of health in recent decades. The problem of the nation's health is clearly set forth in the report of President Eisenhower's Commission on National Goals.[7] It states, ". . . we must have more doctors, nurses, and other medical personnel . . . more hospitals, clinics and nursing homes. . . . Extension of medical insurance is necessary, through both public and private agencies. . . . Federal grants for construction of hospitals should be continued and extended to other medical facilities. Increased private, state and federal support is necessary for training doctors. . . ." Medical school enrollment, which must rise 50 per cent by 1970, should be encouraged by scholarships for men and women of talent and modest means. Greater efficiency in present medical institutions would help reduce the need for new ones.

Although the report avoids the subject, one member of the Commission urges extension of Social Security for the health needs of the aged as a "logical choice". "Social Security," he said, "is becoming a major factor in meeting minimum needs for older people and it is

logical to include provision of health services in the same administrative machinery."

While it is stated that the Commission's report is not offered as a blueprint for legislative action, but rather as a "consensus of aims", it is well to point out that our attitude towards medical care over the past 60 years has been changing. As late as 1900, most health problems were a matter of personal responsibility, and any assumption of this responsibility by government was considered an infringement upon "personal liberty". However, as better medicine has become available, and as more and more people have become aware of its importance to their welfare, demands for medical services have increased.

The task of meeting these demands has become too great for voluntary and private groups. As a result, governmental bodies at all levels —village, municipal, state, and federal—are becoming more and more concerned with matters of health. This is further reflected in the attention directed to health by all branches of government—the legislative, the judicial, and the executive. How far should this movement continue? Should matters of health be the sole responsibility of government? Should taxation meet all the costs? If the government controls the purse strings, will it dominate the profession? Regardless of how these questions may be answered, it appears that medicine is headed for increasing political control by a government that has adopted much of the spirit, if not the letter, of socialism. In a society where class distinctions are being obliterated, this places an increasing responsibility upon the medical profession. It is a responsibility that merits the best in understanding, reasoning, and wise decisions, presented to the country in an articulate and straightforward manner.

Under the atmosphere of these trends toward increasing goverment support and control, there is, among certain lay organizations, an unmistakable nucleus favoring socialization of medicine in a form similar to that provided in Great Britain's National Health Act of November 1946.[8] The New York Academy of Medicine has and will continue to further the concept that the philosophy and policies of the practice of medicine should be determined from within the medical profession, not from without. Furthermore, it holds that the profession should keep its house in order by being alert to recognize and meet—as they arise—problems that concern it solely and those involving it with other groups of society.

I have indicated some of medicine's increasing responsibilities and how they lend themselves to evaluation under the headings: scientific, sociologic, economic, and political. By grouping the problems inherent in these responsibilities and attacking them by tactics most adaptable to each category, it is hoped that solutions may be found that will both meet the objectives of the profession and be accepted by those other segments of society that are most intimately concerned. In many of the problems that arise, the Academy has not only a vital interest but, with your participation, may have a major contribution to offer. These are representative of the tasks undertaken under the guidance of the Council. You, the Fellows of the Academy, are best equipped to solve them. The Council and I seek and anticipate your continued cooperation in the furtherance of a program that will enable the Academy to meet present day demands, while concomitantly planning for the future.

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CITATION AND PRESENTATION

OF THE

ACADEMY MEDAL

TO

ELMER VERNER McCOLLUM, Ph.D., Sc.D., LL.D.

H. D. KRUSE

Executive Secretary, Committee on Public Health
The New York Academy of Medicine

FOR the fifteenth time in thirty-two years The New York Academy of Medicine is awarding its Medal. To the select and distinguished list of recipients is to be added one of the most widely known and outstanding scientists of our day, Elmer Verner McCollum.

His life has been enviable in that it has been doubly satisfying. What more could any man want than to render service to his fellow man while following the quest for knowledge?

After receiving his doctorate at Yale, McCollum worked briefly with T. B. Osborne on the chemical analysis of protein. Then he was invited by Professor E. B. Hart to join the staff of the Wisconsin Agricultural Experiment Station. There a pretentious study, planned by S. M. Babcock and begun in 1906 under Hart, was under way. In this experiment the objective was to determine whether three rations, each derived from a different plant, corn, wheat and oats, and prepared to be equivalent in their content of protein, carbohydrate and fat, would prove to be of equal nutritive value for growth, maintenance, and reproduction of cattle. McCollum was to be the biochemist in the group of investigators.

At this point it is informative to review the principles of nutrition prevailing at that time. Diets were believed to be adequate for promotion of growth, development, and other biological processes if they

ELMER VERNER MCCOLLUM, PH.D., SC.D., LL.D.

provided sufficient energy, protein, carbohydrate and fat. Few were concerned about testing the validity of these teachings.

As the experiment progressed it became apparent that despite the apparent similarity in nutrient content, as determined by chemical analysis, of the three rations, they had distinctly different effects on the biological performance of the cows as judged by appearance, reproductive records, vitality of the young, and milk production.

McCollum realized that this biological performance was more informative and revealing than the data from hundreds of chemical analyses, but he also was aware that cows had limitations as experimental animals in dietary studies. He needed a small animal with a correspondingly small food intake, a short gestation period, and large litters.

So he turned to albino rats as experimental animals. He tested their ability to grow on a diet containing carbohydrate, fat and protein, according to the recommended dietary requirements of that day. The rats failed. But when he added certain natural foods, the rats' decline in weight was checked, then reversed with subsequent gain. This was a phenomenon not explained by any of the then accepted scientific principles. Upon consulting the literature he found that a few earlier investigators had reported failure to obtain growth in mice on carbohydrate, fat, protein and salts. But no one until McCollum had overcome this difficulty by addition of supplements. He concluded that the supplement contained a hitherto unrecognized dietary essential. Since it was associated with the fat component, he called it fat-soluble A.

About two decades before this demonstration, a little-known discovery, which was to have a bearing on McCollum's work, had occurred on the other side of the world. Beriberi, a disease affecting the peripheral nerves, was widely prevalent in different parts of the world, among them Java. Christiaan Eijkman was one of several investigators who were attempting to discover the cause of it. While working in the hospital at Weltevreden, Batavia, he noticed that fowls fed scraps from the hospital table developed what appeared to be an analogue of beriberi. To this he gave the name polyneuritis gallinarum. He was able to reproduce the condition at will by feeding polished rice to the fowl. Thus he was the first to induce a deficiency disease experimentally in animals.

But his thinking was so completely bound by the then dominant bacteriological and toxicological viewpoint that he elaborated an explanation in accordance with it. He believed that polyneuritis was the result of a toxin and that the silverskin layer of the rice kernel contained an antitoxin against it. It remained for Grijns, his successor, to demonstrate that a deficiency, not a toxin, in the diet induced polyneuritis and to first enunciate the theory of a deficiency disease. Both Eijkman's and Grijns' reports of their work were published in a Dutch journal and therefore did not receive immediate widespread attention.

Casimir Funk focused attention on the Eijkman-Grijns dietary essential with his attempts to isolate it from rice. But his principal contribution was in neologism; he coined the word "vitamine" for the substance.

It should be pointed out that although Eijkman, Grijns, and McCollum in common used the dietary approach in their experimental studies, the former two were seeking the cause of a disease while McCollum was searching for the explanation of failure in growth. Finally, the parallel lines converged as McCollum demonstrated that rats on a purified diet not only failed to grow and lost weight, but developed a specific disease which could be overcome or prevented by an appropriate supplement containing the missing dietary essential. This relationship was revealed when he discovered that his water-soluable B factor was the same as Eijkman's and Grijns' antineuritic vitamin.

It was also shown that animals lacking his fat-soluble A not only failed in growth but developed an ocular disease called xerophthalmia.

At that time the School of Hygiene and Public Health was being established in The Johns Hopkins University. It was typical of the unconventionality of William Henry Welch, the first Director, that his first two appointments were nonmedical scientists from agricultural experiment stations—Raymond Pearl from Maine, and E. V. McCollum from Wisconsin.

Once established in Baltimore, McCollum in conjunction with Park and Shipley turned his attention to rickets and the possibility that it was a deficiency disease. Finally, success crowned their efforts when it was demonstrated that rickets could indeed be induced by dietary means

and that it was prevented and cured by the then newest vitamin, the antirachitic Vitamin D.

The basic objective of McCollum throughout his scientific career has been to answer the question "How many dietary essentials are there and what are they?" He aimed to demonstrate the number and to identify them. At this point he turned his attention to the possible indispensability of elements known to be present in food, but whose biological essentiality was yet undemonstrated. In succession he studied diets deficient in manganese, magnesium, potassium, sodium, and zinc, the so-called trace elements.

The hallmark of the elite among investigators is originality, perceptiveness, and consistently successful performance. Judged by these criteria, McCollum is a truly outstanding investigator.

Immersed throughout his scientific career in fruitful research in what was one of the most exciting periods in medical history, McCollum nevertheless was not a cloistered laboratorian interested solely in investigation. He was equally concerned with the application of the new dietary facts, much of which he was revealing. He had the ability to carry the newer knowledge to the people by putting it in language which everyone understood. He coined graphic and easily remembered phrases such as "protective foods", "Eat what you should, then eat what you want". His book with that wonderful, alliterative title, THE NEWER KNOWLEDGE OF NUTRITION, was the authority on the subject.

Few developments have had such far-reaching beneficent consequences as the new science of nutrition. When the amazing and spectacular prolongation of life expectancy is mentioned, better nutrition is invariably assigned a leading place as one of the most influential factors. It was McCollum who found the lost horizon. Through his researches he virtually rewrote the science of nutrition. His work marked the beginning of an era that is not yet ended. It is no exaggeration to say that he has contributed more to our newer understanding of nutrition than any other man. Millions of his fellow men are indebted to him for their life and happiness.

Numerous honors have already been showered upon him with national and international recognition: membership in many scientific

societies, both here and abroad, with high office in several of them; invited participant to important international conferences; at least eight medals; and a number of other awards.

It is a privilege and honor for The New York Academy of Medicine to award its Medal to this distinguished man.

Accompanying the Medal is this citation:

TO ELMER VERNER MC COLLUM, BIOLOGICAL AND MEDICAL SCIENTIST, EDUCATOR,

IN RECOGNITION OF HIS BASIC RESEARCH WHICH USHERED IN THE ERA OF THE NEWER KNOWLEDGE OF NUTRITION; OF HIS FRUITFUL EFFORTS WHICH CONTRIBUTED TO THE ERADICATION OF DEFICIENCY DISEASES; OF HIS DEMONSTRATION OF THE TREMENDOUS SIGNIFICANCE OF NUTRITION, NOT JUST FOR THE PREVENTION OF DISEASE, BUT ALSO FOR THE PROMOTION OF HEALTH AND PROLONGATION OF LIFE; AND OF HIS INFLUENCE UPON THE DIETARY HABITS OF MAN THROUGHOUT THE WORLD THROUGH HIS RESEARCH, WRITING, AND TEACHING.

CITATION AND PRESENTATION OF THE ACADEMY PLAQUE TO GEORGE BAEHR, M.D.

HOWARD REID CRAIG
Director, The New York Academy of Medicine

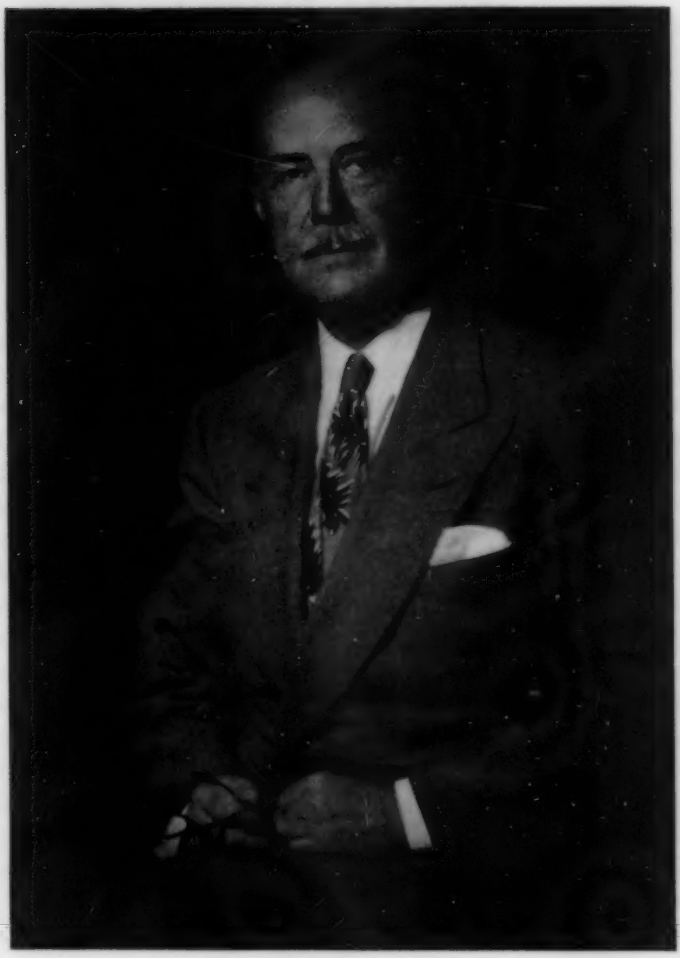
IT is my privilege to present, on behalf of the Committee on Honors, this plaque which is awarded as a token of appreciation for outstanding services and contributions to the life of The New York Academy of Medicine.

Tonight's recipient is a many-faceted individual with brilliant careers in many medical fields. A graduate of the College of Physicians and Surgeons, Columbia University, he entered military service in World War I and, in his very early thirties, held the rank of Lieutenant Colonel in command of U.S. Base Hospital No. 3 in France. He also served in the Near East on the commission studying the cause and control of typhus fever. In World War II he became a Medical Director in the U.S. Public Health Service with the rank of Colonel, and then Chief Medical Officer of the U.S. Office of Civilian Defense.

Between these two wars in which he had so distinguished himself, he had established himself as a pathologist of the first rank and as a brilliant, astute clinician and teacher. His contributions in these fields, and particularly in the area of collagen diseases, have been great in number, varied in character, and sound in observation and reasoning. As a result, he was made Chief of the First Medical Service and Director of Clinical Research at The Mount Sinai Hospital, and Clinical Professor of Medicine at the College of Physicians and Surgeons.

Always intensely interested in the overall problems of medical care for our whole population, he was one of the founders of the Health Insurance Plan of Greater New York and from 1950 to 1957 was its President and Medical Director.

As Chairman of the Executive Committee of the National Conference on Nomenclature of Diseases and the Editorial Advisory Board of the Standard Nomenclature of Diseases and Operations, he contributed



GEORGE BAEHR, M.D.

greatly to bringing order out of the chaos of nomenclatural practices.

As Officer, Trustee or Director, he has served innumerable agencies in the fields of community welfare, philanthropy, and health. Under four successive Mayors of New York City he has served as a member of the Board of Health or the Board of Hospitals and, at one time, on both Boards. By appointment of four successive Governors of this State, he has served for 25 years as a member of the State Public Health Council and at present is Chairman of that Council.

A Fellow of The New York Academy of Medicine for forty-two years, Dr. George Baehr has served the Academy with the same unstinting zeal, enthusiasm and devotion that he has manifested in his other activities. For thirty years he served as an active and valuable contributing member of the Committee on Public Health Relations and for ten years was that Committee's Chairman. He is now an Emeritus Member but, because of his interest, often attends its meetings.

From 1945 to 1948, Dr. Baehr was President of this Academy. It was during his term in office that the Academy celebrated its Centenary, and it was during his tenure that the present Director took office. This fact is particularly noted, for it gives the Director an opportunity to express publicly his gratitude to Dr. Baehr for the help, the guidance and the patience he showed to a new, inexperienced but avidly willing executive.

For ten years following his Presidency, Dr. Baehr served on the Board of Trustees of the Academy, contributing particularly to the deliberations of its Executive or Finance Committee.

A man of imagination, of courage, who does right as he sees the right, one who demands as much of himself as he does of others, one who employs his great talents for the good of the community as well as of medicine, the Academy does itself honor in bespeaking its appreciation for his long years of devoted service in its interests.

Speaking for the Committee on Honors and on behalf of The New York Academy of Medicine, it gives me great personal satisfaction to present the Academy Plaque on which is inscribed:

PRESENTED TO
GEORGE BAEHR
IN RECOGNITION OF
OUTSTANDING SERVICE TO
THE NEW YORK ACADEMY OF MEDICINE

RADIATION AND PUBLIC HEALTH*

L. E. BURNEY

Surgeon General, Public Health Service
U. S. Department of Health, Education, and Welfare

JUST THREE decades ago, the Public Health Service participated in an investigation of what was then considered a medical oddity, lodged in a rather obscure corner of the broad field of industrial hygiene – the poisoning of a group of watch-dial painters who had, unknowingly, ingested considerable quantities of radium by moistening their paintbrushes with their tongue and lips.

Now, only 30 years later, within the professional lifespan of many of us here tonight, that investigation has acquired status as a pioneering study in one of the broadest and most rapidly growing fields of public health–the field of radiological health protection.

Nothing, I think, better illustrates the dynamic nature of the society we serve than the sudden upsweep into prominence of environmental health problems in general and radiological health problems in particular. As physicians we have been drawn into this new world of circumstances largely beyond our control.

I am sure many of you share my frequent bewilderment at the new dimensions of the health sciences, and the vast new areas of competence with which we must become acquainted if we are to remain literate in our own profession. I find myself engaged in meetings with nuclear physicists discussing ionizing radiation, with meteorologists discussing air pollution, with aquatic biologists discussing water pollution. All of these things seem infinitely far removed from the medical curriculum through which we passed 20 to 30 years ago. Yet they are fundamental to the health of the American people in the coming years.

For this reason I am especially pleased to be meeting with this distinguished Academy this evening, and to discuss with you some of the public health implications of ionizing radiations in the environment. Many of these implications are still dimly seen–despite an enormous

* Presented at the combined meeting of the Sections on Medicine and Surgery with the Stated Meeting of The New York Academy of Medicine, December 1, 1960.

and rapidly accelerating research effort, we are still dealing here at the edge of darkness. Nevertheless, we can at least discern the outlines of the principal problem areas, the avenues of approach now being explored, and some of the responsibilities incumbent upon us as physicians in a nuclear age.

Dr. Russell Morgan, of the Department of Radiological Science of the Johns Hopkins School of Hygiene and Public Health, pointed out recently in a lecture to the American Academy of Preventive Medicine that the radiological health program now developing is almost unique in the annals of public health:

> "Historically, major public health programs have developed after it has been amply demonstrated that a health problem involving substantial mortality and/or morbidity exists. In the radiation field, however . . . the overt evidence of a radiation health problem in the world today is so small that one may be justified in asking why so much attention is being given to it."

Many reasons underlie the apparent paradox of excessive concern over a public health problem not yet obvious in terms of widespread damage. Unquestionably the highly emotional overtones of the problem —in terms both of its association with nuclear war and its implicit threat to future generations—have forced it upon the public consciousness and conscience.

But there are compelling scientific reasons as well, having to do with the nature of the problem itself. If we are to deal successfully with radiological health, we cannot wait for substantial rates of mortality and morbidity unmistakably attributable to ionizing radiations. Clinical evidence of radiation damage accumulates too slowly, and radiation in the environment is increasing too rapidly, to permit us the luxury of delay.

Before examining the nature and scope of public health programs now under way, let us review briefly some of the basic facts of life with radiations.

We are exposed to natural low-level radiation from cosmic rays and from the terrestrial radiation emitted by the uranium, thorium, and actinium series of elements in the earth's crust. This radiation has been radiating onto, and from, our planet since long before life first emerged. As far as it is possible to ascertain, it has caused no gross interference with the vital functioning of the human population, even in areas where the levels are highest.

We are exposed to man-made low-level radiation from x-rays, reactors, particle accelerators, and radioisotopes, used in a variety of beneficial ways. The largest single source of exposure of significance to the general population seems to be the use of medical and dental x-rays.

A few figures recently developed by the National Advisory Committee on Radiation convey some impression of the rate at which man-made radiations are increasing and may be expected to increase in the environment. In the three decades between 1925 and 1955, the estimated annual whole body x-ray dose received by the average individual increased 900 per cent—from 15 to 153 millirems per year. In the six-year period 1952-1958, the number of users of radioisotopes in medicine increased from 445 to nearly 2,000. And, as a forecast of things to come in the field of nuclear power, it has been estimated that the accumulated volume of radioactive wastes from nuclear installations, including high and intermediate level wastes, will increase from about 1.5 *million* gallons in 1965 to 2 *billion* gallons in 1995.

Our knowledge of the effects of low-level radiation on man is grossly inadequate, but we do know that when a biological system is exposed to sub-atomic particles like alpha, beta, or neutron emanations —or to gamma radiation or x-rays—there occurs an interaction between a high-energy physical system and a low-energy biological system, with completely different consequences. The alpha particle ejected from a disintegrating radium nucleus, for example, will deliver 5 to 10 million electron volts of energy; ordinary ionic exchanges in living matter involve, on the average, only 5 to 10 electron volts.

We know far more about higher dose levels, up to and including lethal doses, than we know about low-level doses. This knowledge comes from study of Hiroshima and Nagasaki victims and from the few nuclear accidents which have occurred, buttressed by extensive animal experimentation. For example, we know, in the case of high-level whole-body irradiation of humans occurring within a short time interval, that some deaths begin to occur at a dosage somewhere between 200 and 400 roentgens, followed by a rise in the death rate with the increasing dose until about the level of 600 to 1000 roentgens is reached, at which point practically none survive.

In fact, a tremendous amount of research has been done and a great deal is known about the health effects of ionizing radiations in relatively

heavy dosages. It is well established, for example, that exposure to high but sub-lethal levels of radiation has three different kinds of deleterious health effects on groups of laboratory animals: an increased frequency of genetic mutations; carcinogenesis; and a general shortening of average lifespan.

Whether or not threshold levels for these effects exist, and if so what they are, comprise one of the most important of our research problems. Meanwhile we are compelled to assume, first, that any radiation is harmful at the cell or tissue level; second, that damage done is to a certain degree irreversible; and third, therefore, that radiation damage is cumulative.

The genetic effects result from irradiation of the reproductive organs. Since lifetime dosage may be considered cumulative, it is apparent that radiation exposure to the gonads should be kept to a minimum from childhood through the family-forming years. Although the quantitative relationship between low doses of radiation and genetic effects is not established with any degree of precision, it has been estimated that a large population exposure dose of 30 to 80 roentgens to the gonads prior to reproduction doubles the probability that a mutation will occur in subsequent generations.

The somatic effects of relatively small doses of radiation are caused by irradiation of various organs. They may lead to the development of leukemia, skin cancer and bone cancer. In general, as with the genetic effects, the somatic effect is greater when the radiation dose is higher.

The biochemical effect of ionizing radiation is a generalized acceleration of the aging process and a life-shortening effect. The mechanism of this phenomenon is presently not understood, but its existence has been demonstrated repeatedly with laboratory animals.

Although human beings, and indeed all living things, have been subjected to natural radiation since the first appearance of life on earth, it appears that there is no effective accommodation between the body and radiations such as that which exists between humans and pathogenic organisms. Experimental evidence suggests that exposure to and recovery from one dose of radiation decreases, rather than increases, the resistance to a second exposure. It is this irreversible component of radiation damage which compels us to be concerned with low levels of exposure.

Faced with a problem of this nature, the health professions have a clear responsibility to proceed simultaneously along three general lines.

The first of these is to acquire, as rapidly as possible, new knowledge of the medical effects of radiation, with special attention to long-term impact of low levels of exposure. This research effort, obviously, has laboratory, clinical and epidemiological components.

The second principal line of attack is the constant monitoring of the environment—maintaining a continuous record of exposures experienced by the population through air, water, milk and food.

The third imperative is to exercise all possible control over man-made radiation so as to eliminate or reduce to a minimum unnecessary exposures wherever they may occur.

Programs in these three areas of research, monitoring and control are moving forward at a rapidly accelerating pace. I should like to describe our Public Health Service radiological health program for you in some detail. In so doing, however, I certainly do not wish to imply that we are the only agency or organization in the field. One of the most hopeful signs in the field of radiological health is the fact that many Federal agencies, state and local health departments, professional groups and private organizations—running across the entire spectrum of our health resources—are participating actively in this national effort.

The Public Health Service Program

Our present deep involvement in radiological health is not a totally new preoccupation. The history of this involvement goes much farther back than many of you, probably, realize. In 1923, the PHS made physical examinations of Bureau of Standards workers handling radium. In 1930, as I have already noted, the Service participated in an investigation of the much-publicized radium poisoning of clock- and watch-dial painters. In 1940, we reported on radium and x-ray hazards in hospitals.

During World War II, data provided by the Service were taken into account by the Manhattan District when that agency—then a top secret operation—was researching the problem of human tolerance to radiation.

In 1945, the fission bomb literally exploded into the awareness of the general public, and the environmental-health problem of ionizing radiation started a faster enlargement. The fusion bomb followed, and it may surprise some of you to learn that, from July 1945 through November 1958, there were no less than 245 announced nuclear detonations, world-wide.

Despite this startling statistic, the genetically significant radiation exposure of the public by means of the fall-out resulting from international nuclear detonations has, up to now, been far outweighed by that resulting from other sources, including diagnostic and therapeutic use of x-rays, the operation of nuclear reactors and particle accelerators, and the use of radioisotopes by industry and the healing arts.

Until 1959, the Service's radiological health activities functioned under the basic Public Health Service Act, which provides broad authority to protect the public in this area, without calling the area by name. The Federal Water Pollution Control Act and the Air Pollution Research and Technical Assistance Act provided ancillary authority.

In 1959, however, our general responsibility became specific. In August of that year, the President established the Federal Radiation Council, comprising the Secretaries of Defense; Commerce; Labor; Health, Education, and Welfare; and the Chairman of the Atomic Energy Commission. The Secretary of HEW was designated Chairman, and the President assigned to HEW the "primary responsibility within the Executive Branch" for radiological health operations. In that same month, the Secretary of HEW reassigned the major portion of this responsibility to the Public Health Service.

Radiological Intelligence Network

We have now in operation three regional radiological health laboratories which, with the Sanitary Engineering Center in Cincinnati, are the keystones of our monitoring program. One of these was opened a year ago at Las Vegas; another last February in Montgomery, Alabama; a third is about to begin operations in Rockville, Maryland. These are the first-generation members of an intelligence network which—now and from now on—will keep a watchful eye on the levels of radioactivity, nationwide, in air, water, food, and milk and on the safety of x-ray apparatus. The Nevada and Alabama facilities analyze and test environmental and biological samples collected by Federal, State, and local health authorities. They also have initiated studies of total dietary intake of radioactivity at selected locations. The Maryland installation will concentrate on health problems arising out of the use of x-rays and on methods for their reduction. This trio serves all 50 states, taking a tremendous load off our Sanitary Engineering Center in Cincinnati, where such testing and analyzing had formerly been done, enabling an

expansion in the radiochemical and radiobiological research conducted there.

The milk-monitoring programs under way for several years have now been expanded, with the number of sampling points increased from the original 10 to 59, each of them collecting monthly milk samples and forwarding them to our facilities for analysis for several radioisotopes, including Sr^{90} and I^{131}. Similar monitoring is being made, nation-wide, of water, air, and foods other than milk, as part of keeping a close check on the radioactivity in our total environment. I am glad to say that the average amounts of radioactivity we are finding in these environmental components are well below the levels designated as safe by various scientific advisory bodies.

The Research Program

Research in a field as broad and complex as radiological health calls for the coordinated work of many disciplines and the support of many agencies and organizations. Fortunately, such a team approach is developing rapidly. The central objective of our own radiological health research is to determine the somatic and genetic effects of low levels of radiation on humans.

The Atomic Energy Commission has, for many years, conducted and supported an intensive laboratory research program which has yielded much of the basic data upon which our present assumptions are based. Other agencies have also been supporting fundamental research; a notable example is the work of the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, supported by the National Science Foundation. Public Health Service support of research, in large measure through grants to investigators outside the Service itself, is being developed in such a way as to complement work already under way.

At the same time, the Service has a rapidly growing intramural research program, of which the following are among the more significant projects now in progress:

- Work in medical epidemiology includes an investigation into the health status of offspring of 20,000 patients subjected to x-ray pelvimetry during their pregnancies. This study includes matched controls.

- A national collaborative study among medical centers throughout

the country is being formulated to investigate the late effects of treatment of hyperthyroidism with radioactive iodine among about 40,000 cases and controls. Of particular interest is the incidence of neoplasia and leukemias. Ancillary objectives of the study include a detailed comparison of the results of surgical as opposed to radioactive thyroid ablation in the treatment of thyrotoxicosis, considering such questions as: dose requirements, expected time intervals to response, and complications such as exophthalmos and myxedema.

• A tri-state study is under way of the relationship between malformations and natural environmental radiation. Vital records, hospital records, and special hospitals will provide data. Sole reliance will not be placed on geological mapping from which levels of radiation may be inferred. Extensive measurements of levels of internal and external sources of radiation exposure will also be made. Interviews of sample cases and control families will be conducted to determine the possible influence of such other etiologic factors as the occurrence of disease in pregnancy, family history of malformation, etc.

• The human population in communities receiving water from the Animas River in the southwestern U. S. is under intensive investigation. This study is a result of detection of higher-than-normal levels of radium in the drinking water in this river, due to radioactive wastes discharged from uranium ore-processing. Measurement of radioactivity in typical diets, excreta, and bone samples from autopsies and surgical procedures will be performed in an attempt to determine the body burden of internally deposited nuclides.

• Demographic and epidemiologic data are being obtained to determine if there has occurred any increase in leukemia, bone sarcoma, or other diseases in which radiation may have been a factor. The size of this population is small, and certain difficulties, involved in applying to an entire population the measurements made of a few families, remain to be solved.

• A survey has been carried out in cooperation with the National Office of Vital Statistics in an attempt to determine the history of medical and dental x-ray exposure of women during the year immediately preceding the birth of a child. Five hundred birth certificates were selected on a systematic random basis. The response to a mailed questionnaire has been excellent. Ninety-eight per cent of the dentists, 96

per cent of the physicians, and 90 per cent of the mothers have furnished information. These results are now being analyzed. Of interest in the preliminary analysis was the finding of x-ray pelvimetry in about 7 per cent of the mothers.

• A different type of survey in a large metropolitan area is under way to ascertain the frequency and type of exposure to medical sources of radiation. This is being correlated with other work to determine the absorbed dose from various roentgenographic and fluoroscopic procedures to certain critical organs, such as the gonads and the bone marrow.

• Physicians in selected areas are collecting and forwarding bone samples from autopsies of stillborn infants, children, and adults to be analyzed for strontium-90 and, in some cases, radium.

Controlling Unnecessary Radiation Exposure

In the area of control, the primary responsibility devolves upon those who are using radiation. Radiological safety programs in industry, developed in close cooperation with the Atomic Energy Commission, are carefully built into the operations of the plants where such programs are needed. It is with the medical and dental uses of x-ray, which, as I have noted, are responsible for the largest share of genetically significant exposure to the general population, that the Public Health Service has been principally concerned.

Today, we, and the country's physicians, dentists, and health officers, are engaged in an expanding cooperative effort to insure that unnecessary exposure is being avoided. Precautions are being redoubled to make certain that machines are properly adjusted and that personnel operating them are thoroughly trained. In addition, many health departments are requiring registration of all x-ray machines in the areas under their jurisdiction. However, the existence of an estimated 200,000 x-ray machines throughout the nation, 90,000 of which are dental x-ray units, indicates the magnitude of the problem of inspection. The major limiting factor is, of course, the continuing national shortage of personnel adequately trained to perform and supervise these highly technical activities.

Chest x-rays constitute a basic technique in the detection of pulmonary tuberculosis, but now, more and more, they are used only in

areas or groups known to have a high tuberculosis incidence. Elsewhere, the tuberculin skin test is used as an initial screening technique, with x-rays given only to positive reactors to the skin test.

The Public Health Service, in its own hospitals and clinics, takes special precautions to protect patients from unnecessary exposure, and operating personnel from all exposure, during the use of x-ray equipment. Many studies have shown that the radiation exposures to the public from medical and dental diagnostic x-ray studies can, by adhering to certain radiological safety criteria, be markedly reduced without reducing the use of x-rays and without detracting from the quality of the examination—even enhancing the quality of the study in many cases.

For the past two years, we have maintained a continual monitoring system in our own installations. Film badges which register radiological exposure are worn by radiographic personnel. These film badges are developed monthly, and, if any excessive exposure shows up, an exhaustive examination of the equipment and procedures involved is made. There has been a marked reduction in exposure since this monitoring system went into effect.

Another project is our development and employment of a new method for evaluating dental x-ray machines used in private offices and clinics, nation-wide. It is a big stride forward, for it enables us to make an entire state-wide survey entirely through the mails. In fact, we call it the "Mail Order Survey". The Public Health Service sends a sensitive sheet of film to each dentist or organization in the survey area. After the film has been exposed to the machines under examination, it is simply dropped in the mail by the recipient for return to us in Washington. Through interpretation of the exposed film, we can determine rather well how safe a machine is—and whether any corrective measures need to be taken. By the end of the year, we anticipate that 6,000 dental x-ray units will have been surveyed. We hope to be able to develop similar procedures for use by physicians and hospitals for medical x-ray machines.

Looking to the Future

As we look to the future of radiological health protection in a world which seems certain to become increasingly nuclear-powered and nuclear-oriented, it is evident that there must be the widest possible dis-

persal of competence and responsibility, if we are to realize the maximum benefits of nuclear technology at minimum hazard.

Local control—in the physician's office, in the factory, in the community—is the most effective control. I have mentioned, in passing, that state and local health agencies are making rapid strides in acquiring the competence needed for effective action. To date, however, their interest and willingness have outrun the availablity of personnel qualified to conduct such programs. The National Advisory Committee on Radiation has estimated that by 1970 approximately 5,200 more specialists and technicians trained in radiological procedures will be needed in health agencies, hospitals, universities, and industry.

The Public Health Service is expanding its training program at the Sanitary Engineering Center in Cincinnati and at our three new regional facilities to meet this need. Significantly, one fourth of our radiological health funds in 1960 are being spent on training activities.

Significantly again, Congress has placed $500,000 at our disposal in the 1961 budget for long-term academic support, by means of grants to universities and other institutions, 1) to strengthen and accelerate the training of radiological health specialists at the graduate level, and 2) to initiate "university centers" to bring into sharper focus the multiform aspects of the search for knowledge of the health effects of radiation.

In addition to the need for technicians and specialists in the area of health physics, which these training programs are seeking to meet, there is also an urgent need for physicians capable of assuming a high order of responsibility in the medical aspects of radiological health. Dr. Morgan, in the paper to which I referred earlier, describes this need in these terms:

> "Ability to evaluate radiation problems clearly, to make decisions forthrightly and to lead radiation research and control programs effectively are a few of the characteristics required of these men. We are speaking here of public health physicians who in their fields are well trained and as capable as the specialists of such fields as surgery, internal medicine, and pediatrics."

He goes on to recommend urgently that Schools of Public Health establish proper curricula for radiation health specialists as soon as possible, noting that ". . . with their rich contacts with academic medicine these schools should be able to provide a superb climate for training in radiological health".

But over and above these requirements for specialists in the medical aspects of radiation, there is, it seems to me, a special responsibility incumbent upon all of us as physicians.

As medicine has diversified and specialized, and as the paramedical disciplines have assumed steadily increasing importance, many physicians have become, to a certain degree, administrators of a health team. We depend upon, and are responsible for, a battery of supporting services of which the various techniques related to radiation are an important segment. By becoming thoroughly informed himself, and by exercising his prerogative as an administrator, the individual physician can insure that in the x-ray procedures under his control the cardinal points of safe practice are observed. He can ask:

Is this x-ray examination truly necessary? Has the need been weighed against the hazard? Has the machine been checked for output and possible leakage? Is it properly filtered, coned and collimated? Is optimum use being made of the three main factors of protection—time, distance, and shielding? Is special attention given to proper shielding in the gonadal area?

By assuring himself that these questions are affirmatively answered, the physician contributes to the full realization of the immense benefits derived from the judicious use of x-rays in the healing arts, eliminating unnecessary exposure at one extreme and unnecessary avoidance of x-ray at the other.

Finally, it seems to me that the physician has an additional responsibility to serve as an informed citizen of his community in regard to the health effects of radiation. Physicians, individually and through their organizations, are influential, and our influence will be very important in relation to radiological health. Many of the basic decisions concerning the nuclear future are not ours to make; they are economic and social decisions in which the voice of medicine is one among many. But it is our task to make sure that our voice is heard, that the health factors are entered into the equations, that the economic decisions are made in terms of biological reality.

René Dubos, in a recent issue of *Harper's Magazine*, put the challenge squarely to the medical profession:

> "It will take great medical statesmanship to protect the fundamental biological rights of man from the threats which are inherent in the Second Industrial Revolution. . . . Modern man will need the guidance of physicians

to achieve fitness of body and mind to his new physical and social environment. The more complex and dependent on technology society becomes, the more urgent it is for modern medical science to determine what must be done to make the world biologically safe—not only for ourselves, but also for future generations."

Because of my confidence in the ability of my profession to move with the moving health frontiers, I am not one of the "prophets of doom" about radiation. Instead, I am prophesying that the medical profession, led by groups such as yours, will adapt itself to the new challenges, and will help to assure that the population moves safely through the nuclear revolution of our time.

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April 4	PANCREATIC DISEASES Henry D. Janowitz College of Physicians and Surgeons Columbia University
April 11	ULCERATIVE COLITIS Marvin H. Sleisenger Cornell University Medical College
April 18	MALABSORPTION O. D. Kowlessar Cornell University Medical College
April 25	JAUNDICE Irwin M. Arias Albert Einstein College of Medicine Fenton Schaffner College of Physicians and Surgeons Columbia University

ADVANCES IN THE MANAGEMENT OF LYMPHOMAS

*Transcription of a Panel Meeting on Therapeutics**

CLAUDE E. FORKNER . . . Moderator

Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, The New York Hospital

Panel Members

JOSEPH H. BURCHENAL

Chief, Division of Clinical Chemotherapy, Sloan-Kettering Institute; Professor of Medicine, Cornell University Medical College; Attending Physician, Memorial and James Ewing Hospitals

MILTON FRIEDMAN

Professor of Clinical Radiology, New York University School of Medicine; Attending Radiation Therapist, Hospital for Joint Diseases and Bellevue Hospital

ALFRED GELLHORN

Professor of Medicine, College of Physicians and Surgeons, Columbia University; Chief, Medical Service and Visiting Physician, Francis Delafield Hospital

DAVID A. KARNOFSKY

Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, Memorial and James Ewing Hospitals

* Presented at the Monthly Panel Meeting (Seventh Series), at The New York Academy of Medicine.

MODERATOR FORKNER: Before starting the panel discussion, I shall delineate the subject a bit. May I have the first slide—

(Slide) This is a classification which depicts the relationship between the diseases we are to discuss. At the top are the leukemic disorders, including so-called plasma cell leukemia, myelocytic leukemia, lymphocytic leukemia, lymphoblastic lymphosarcoma, giant follicular lymphosarcoma, reticulum cell lymphosarcoma, and Hodgkin's disease of three varieties. You will see that these diseases somewhat overlap. Lymphoblastoma, or malignant lymphoma, is a general term which includes lymphocytic leukemia, leukosarcoma, the varieties of lymphosarcoma, and the three varieties of Hodgkin's disease. Lymphocytic leukemia and lymphocytic lymphosarcoma are perhaps the same disease. If one follows the patients having chronic lymphocytic leukemia for a long enough period, at least 50 per cent of them will eventually exhibit a leukemic blood picture. We do not know the cause of any of these diseases. They are all disorders which are invasive, behaving like tumors. As lymphoblastoma involves the lymph nodes it tends to destroy their normal architecture. Some of the lymphoblastomas tend to invade the blood stream whereas others do not.

Hodgkin's disease has certain other characteristics, the presence of so-called Dorothy Reed or Sternberg cells, the presence often of eosinophils and of fibrous tissue.

The first effective treatment for this group of diseases was irradiation therapy with x-rays, employed by Pusey in 1902. He thought that he had cured some of these diseases because of remarkable effects, using relatively low doses of irradiation.

Although these disorders behave like malignant disease they are not always rapidly fatal. For example, a patient who died last week at The New York Hospital was first observed to have Hodgkin's disease in 1934. Repeated biopsies confirmed the diagnosis. Yet after 25 years of Hodgkin's disease, she died of chickenpox. At death she had extensive Hodgkin's disease and was markedly debilitated.

Another patient had lymphosarcoma diagnosed by biopsy in 1944. From 1944 to 1952 she was treated with x-rays, but then, for four years, she received no treatment for the lymphosarcoma and, on clinical examination, no evidence of lymphosarcoma was found. She died of another disease 14 years after the original diagnosis. At autopsy only three small nodules of lymphosarcoma were found, one in the

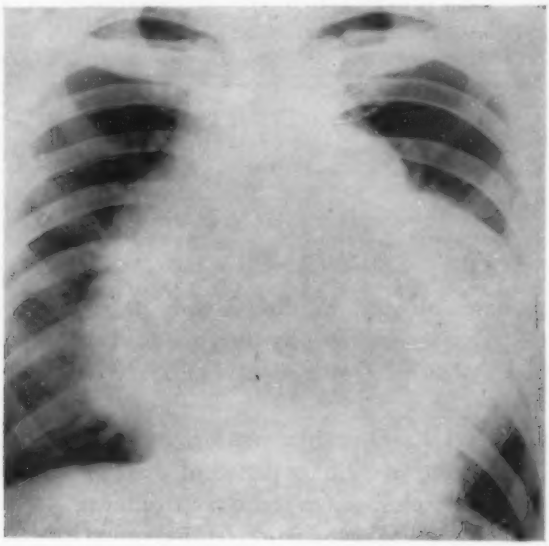

Fig. 1. Mediastinal lymphoma in 1935, before treatment. Patient is free of disease today, 24 years later.

right kidney, and two in the left kidney. The lymph nodes and other tissues were free of the disease.

I mention these cases because it is important to know that people may live for many years after the lymphoblastoma becomes evident. Each of these two patients died of other causes, after having lived many years with the disease.

Dr. Friedman will now discuss therapy with various forms of irradiation.

DR. MILTON FRIEDMAN: Twenty-four years ago a dentist, aged 33 years, came to me for treatment of a large mediastinal tumor (Figure 1). A 200 kv. x-ray machine was used to deliver a tumor dose of 1385 roentgens in 40 days. The mass in his mediastinum disappeared, and he is well today. He is a grandfather. This case illustrates one concept pertaining to most lymphomas. A patient developing a malignant lymphoma is destined to live a certain reduced span of years. This span will be shortened further if the toxic component of the disease debilitates him, or if one of the lesions involves a critical organ such as the spinal cord or the brain. Treatment averts a precipitous death or neutra-

TABLE I—CLINICAL STAGE ON ADMISSION

Stage	*No. of cases*	*Percentage*
I	48	22
II	32	15
III	136	63
Totals	216	100

lizes each recrudescence of the disease with its accompanying toxic factor. If our treatment is efficiently designed to retard the disease, the patient will live for the maximum allotted time, and this can be 25 years or longer.

This case that I have just presented illustrates the fact that the patient was destined to live a long period of time; I do not ascribe his 24 years of survival exclusively to the x-ray treatment.

I would like to tell about an interesting group of 216 cases of Hodgkin's disease, treated during World War II at Walter Reed Army Hospital. It is significant because it is a large number of cases treated in one institution over a period of five years by one individual, and with a consistent policy of irradiation. The lesions were divided into three stages:

CLINICAL CLASSIFICATIONS OF HODGKIN'S DISEASE

Stage I. Limited to a single lymph node group or to a single lesion in any organ, without constitutional symptoms.

Stage II. Disease limited to two adjacent lymph node groups, or to a single organ lesion plus regional lymph node involvement, with or without constitutional symptoms.

Stage III. Involvement of two separate lymph node groups or of multiple groups of lymph nodes, and/or more than one organ involved, with constitutional symptoms.

Note that in Table I almost two-thirds of the patients in this series were in Stage III when first seen. Our overall five-year survival rate—that is survival, with or without disease, from the onset of disease—was 44 per cent.

When based on the date of the first treatment, the five-year survival rate was 37 per cent, one of the highest survival rates reported.

TABLE II—SURVIVAL RATES BASED ON DATE OF ONSET OF DISEASE

Stage	*No. of cases*	*5 year survivals*	*10 year survivals*
I	48 (22%)	29 (60%)	9 (18%)
II	32 (15%)	15 (46%)	7 (21%)
III	136 (63%)	53 (38%)	8 (5%)
Totals	216 (100%)	97 (44%)	24 (11%)

Lost to follow-up and considered dead: Two cases.
Survivors may or may not have active disease.
Longest survivor is living and well 18 years after onset of disease.

TABLE III—SURVIVAL RATES BASED ON DATE OF FIRST X-RAY TREATMENT

Stage	*No. of cases*	*5 year survivors*	*10 year survivors*
I	48 (22%)	24 (50%)	6 (12%)
II	32 (15%)	14 (43%)	3 (9%)
III	136 (63%)	44 (32%)	6 (4%)
Totals	216 (100%)	82 (37%)	15 (6%)

In a series reported from Toronto by Dr. Peters, using similar treatment technique, the five-year survival rate was similar to mine, 38 per cent. The principle of treatment used in both instances was the same, i.e., predominant use of aggressive irradiation.

A few of the Stage III patients who survived more than five years are illustrated in Figures 2 and 3. One patient had infiltration of the lung itself in addition to widespread lymphadenopathy. Some of the patients had constitutional symptoms and bone involvement, and still survived five years. One of the reasons for the high survival rates was that the irradiation was aggressive and extensive. The dose differed from patient to patient according to the radiosensitivity of the tumor. We also irradiated prophylactically the uninvolved cervical, axillary and inguinal lymph nodes, even though it entailed two or three months' treatment with 40 to 90 doses.

The technique of treatment, especially the dose of x-rays, is very important. There is no standard dose of x-rays, because some Hodgkin's disease nodes can be destroyed with 800 r and others may require 3500 r.

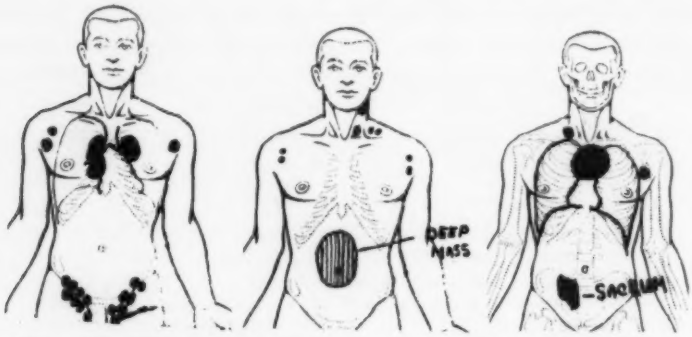

Fig. 2. Examples of Stage III patients who survived *more than five years* following treatment with aggressive irradiation. The patient in the center originally had severe backache caused by the retroperitoneal mass. The patient on the right had a destructive lesion of the right side of the sacrum.

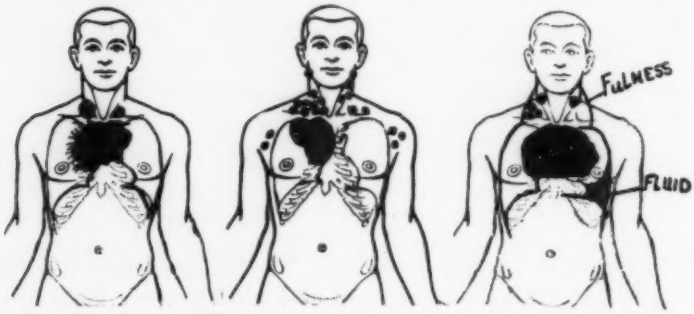

Fig. 3. Examples of Stage III patients who survived *more than five years* following aggressive irradiation. In the patient on the left the disease diffusely invaded the lung.

If the tumor is very radiosensitive, then the six peripheral node areas (cervical, axillary and inguinal) can be irradiated in 18 treatments. If it is resistant, 60 treatments may be required. Thus it is important to ascertain the correct dose for each patient.

We therefore irradiate the first group of nodes with a standard tumor dose of 1200 r in one week. If the tumor is very radiosensitive, it will disappear completely during the first week of treatment. For additional surety, we then bring the total tumor dose up to 1800 r in 10 or 12 days. On the other hand, if the tumor has shrunken only 10 per cent or 15 per cent when examined on the tenth day after the first treatment, it will require the maximum dose (3500 r) for its eradication; and the supplementary irradiation is given over a period of two

to three weeks. Usually, all the nodes in the same patient require similar dosage, except in the terminal few months of the disease when the lesion becomes more resistant. With our technique the irradiated nodes do not recur in 90 per cent of the patients. In the remaining 10 per cent of the cases, the irradiated nodes recur, usually in the terminal phase when the disease becomes fulminating and widespread. When the initial doses are small, recurrence may take place and the new nodes become progressively more radioresistant.

Little or no chemotherapy was given to this series of patients. Dr. Karnofsky was in the Army when he pioneered in the use of nitrogen mustard for lymphoma. He provided us with nitrogen mustard for the treatment of some of the earlier cases. However, very few of our patients received nitrogen mustard. When a patient had one group of nodes, as in the right neck, we irradiated the right and left neck and both axillary and inguinal nodes. It has been questioned whether this prophylactic irradiation is necessary. Our results, as well as those of Dr. Peters, tend to support the procedure used.

The modern supervoltage x-ray machines now enable us to deliver easily the proper dose to the deep nodes in the chest and abdomen when they are involved in the disease process.

To summarize: Improved survival rates are due to three features: aggressive irradiation with the proper dose for each tumor; prophylactic irradiation of the involved nodes; and supervoltage x-rays. In my opinion, nitrogen mustard, with few exceptions, should not be used in the early phase of treatment, even with widespread disease and constitutional symptoms. It should be reserved for the terminal phase of the disease when various chemotherapeutic agents are used.

MODERATOR FORKNER: *Is the supervoltage treatment comparable to the use of a cobalt unit?*

DR. FRIEDMAN: Yes. Cobalt machines give supervoltage x-rays; however, there are very few cobalt machines that are properly designed and constructed. Most of them are compromise apparatuses.

Table IV gives a summary of several reports in the world literature. It illustrates the progressive increase in survival rates when modern irradiation techniques are used.

A current question is, "When should nitrogen mustard be employed?" Our evidence, and that of Peters, relegates the drug to a secondary role, to be used in the terminal phase of the disease or in rare

TABLE IV—HODGKIN'S DISEASE
COMPARATIVE SURVIVAL RATES

Author	*Place*	*Date of Report*	*No. of Cases in Survey*	*Percentage 5 yr. Surv.*	*Percentage 10 yr. Surv.*
Krumbhaar	University of Penn.	1939	—	15%	6%
Slaughter & Craver	Memorial Hospital	1942	265	17.7	3.4
Merner & Stenstrom	Minneapolis	1947	185	21	8
Healy, Amory and Friedman	Walter Reed Army Hosp. Washington	1953	216	37	6
Paterson and Paterson	Christie Hosp.	1954	256	25	—
Levinson et al.	Univ. of Utah	1957	58	31	0
Craver, Diamond and Spitz	Memorial Hospital	1957	713	19.5	7.2
Peters	Toronto Gen. Hospital	1958	291	38	24

situations. Levinson, Wintrobe and associates (1957) find no demonstrable difference between treatment with x-rays or mechlorethamine hydrochloride; however, their published evidence does not strongly support this deduction, especially since they used the drug exclusively in only a few cases and used mostly irradiation.

There is an unfortunate tendency on the part of general practitioners and internists to use conservative chemotherapy early in the course of Hodgkin's disease. This should be discouraged, as the results to date are not as good as with aggressive irradiation.

MODERATOR FORKNER: I have asked Dr. Gellhorn and Dr. Karnofsky to discuss the chemotherapy of this group of diseases.

DR. DAVID A. KARNOFSKY: The emphasis in my discussion this afternoon will be more on the management of the special manifestations and on the different types of lymphomas. Dr. Gellhorn seemed to be in a pessimistic mood when I talked with him earlier. He decided to discuss the toxic effects of chemotherapeutic agents, and I will discuss their therapeutic value.

In the management of lymphomas the most important group of drugs available are the polyfunctional alkylating agents, of which nitrogen mustard is a representative. A point of major importance, before discussing the use of these agents, is to decide how we feel about the variety of polyfunctional alkylating agents available for clinical use.

FIG. 4—VARIATIONS IN PROPERTIES OF HN2 ANALOGUES

CHEMICAL STRUCTURE
CHEMICAL PROPERTIES—
Solubility,
Stability
CHEMICAL REACTIVITY
Various pH's,
Various substrates
NEUROLOGIC EFFECTS—
Convulsive,
Cholinergic,
Psychogenic

FIG. 5—SIMILARITIES IN ACTIVE HN2 ANALOGUES

Alkylating compounds
Two or more functional groups
Mutagenic and carcinogenic activity (when tested)
Bone marrow depression
Tumor growth inhibition
Effects on mammalian tumors in chick embryo

We have to decide whether these agents have important quantitative or qualitative differences in activity or whether they represent a group of drugs with a common mechanism of action.

We have reviewed the properties of these agents, and Figure 4 shows clearly that these derivatives differ greatly in their chemical and acute pharmacological properties. The chemical structures are different. Their chemical properties are different; for example, in their stability in solution, optimal pH at which they react, selective reactivity with different substrates, and acute pharmacological effects, such as convulsive properties, cholinergic effects and production of psychogenic disturbances. There is no question that these various agents have many pharmacological and chemical differences. On the other hand, these compounds have similar activities as concerns their effects on proliferating tissues (Figure 5).

Wherever these effective polyfunctional agents have been studied systematically, certain common activities are found. For optimal effec-

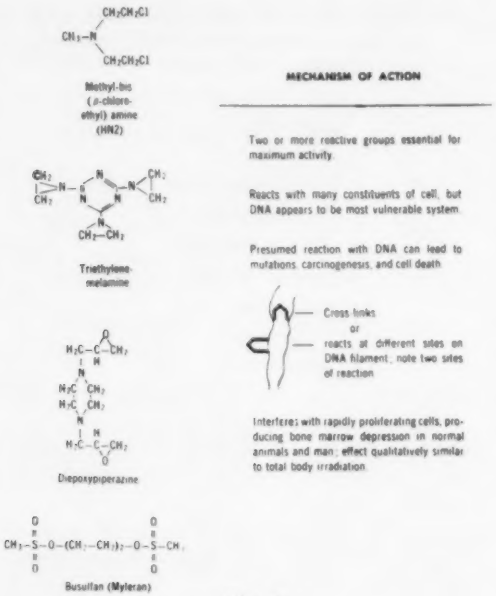
Methyl-bis (β-chloroethyl) amine (HN2)
Triethylenemelamine
Diepoxypiperazine
Busulfan (Myleran)
MECHANISM OF ACTION
Two or more reactive groups essential for maximum activity.
Reacts with many constituents of cell, but DNA appears to be most vulnerable system.
Presumed reaction with DNA can lead to mutations, carcinogenesis, and cell death.
Cross links or reacts at different sites on DNA filament; note two sites of reaction.
Interferes with rapidly proliferating cells, producing bone marrow depression in normal animals and man; effect qualitatively similar to total body irradiation.

Fig. 6.

tiveness they require two or more functional or reactive groups. They are mutagenic in bacteria and Drosophila, and carcinogenic in laboratory animals. In adequate dosage they all produce severe bone marrow depression, intestinal injury and delayed deaths in experimental animals. They inhibit the growth of transplantable tumors in rodents, and, in a special system, they are capable of selectively destroying mammalian tumors growing in the chorio-allantoic membrane of the chick embryo at doses not lethal to the embryo. Thus they have a great deal in common in their biological effects.

There are many different types of alkylating agents available (Figure 6). We have sulfur mustard, which Dr. Louis Alpert has recently studied. He finds that the effects it produces are similar to those produced by nitrogen mustard. We have nitrogen mustard, and a number of related compounds, such as chlorambucil (Leukeran), sarcolysin (Melphalan, PAM) and Endoxan or Cytoxan, ethylamine derivatives such as TEM, Thio-TEPA and E-39, an entirely different type of substance, sulfonyl methane esters such as busulfan (Myleran), which chemically is an alkylating agent. Recently there have been studies with diepoxy-

piperazine, another different chemical which has effects similar to nitrogen mustard. In Germany, another type of nitrogen mustard, Endoxan, has been described, which is said to be less toxic as far as bone marrow depression is concerned, and to have increased evidence of therapeutic activity. From our own experience and from a review of the evidence, I don't believe we can support the view that there is any important difference in the therapeutic effects of these various alkylating agents. They all have the same spectrum of biological activity and they produce therapeutic effects with approximately the same degree of toxicity as far as the patient is concerned. It is conceivable that some day someone may find a nitrogen mustard which will affect lymphomas without producing bone marrow depression. Thus far, however, there is no convincing evidence that we are approaching this situation.

On the other hand, different mustards have various conveniences in use. For example, nitrogen mustard or HN2 is given by intravenous injection, and one can give a rapid course of treatment. TEM can be given intravenously and orally and does not cause nausea and vomiting to the same extent.

Chlorambucil can be given orally by daily administration and one can, in suitable cases, obtain smooth and prolonged control in patients with systemic manifestations of lymphoma. In our opinion, nitrogen mustard and chlorambucil are adequate representatives of the alkylating agents for clinical use.

What are the indications for the use of the polyfunctional alkylating agents in Hodgkin's disease or lymphomas? I would like to cite four situations in which I think they have been useful. The first situation is in early management of Hodgkin's disease. I certainly agree with Dr. Friedman that localized radiotherapy is by far the most effective method of managing this disease. However, in early cases where the disease appeared to be confined to one major area, such as mediastinal and cervical nodes, we have been interested in combining a course of nitrogen mustard intravenously with intensive local radiotherapy. The reasons for this are: first, that there may be some additive local effect from the two forms of treatment; and secondly, if some lymphoma cells are scattered to other areas, perhaps the nitrogen mustard may have some effect in either destroying these cells, or at least delaying the recurrence of the disease. This is an uncertain indication for nitrogen mustard. The combined procedure, however, has done no harm, and possibly it may

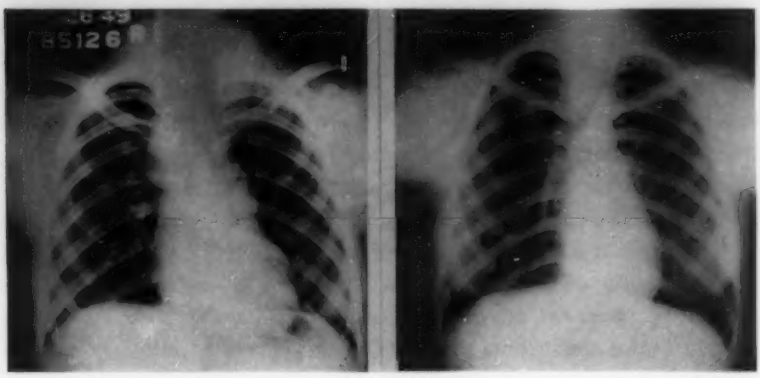

Fig. 7.

produce an increased number of long survivors. This is a matter of many years of study.

An example of this combination is shown in Figure 7. An 11 year old girl received, in 1949, a course of nitrogen mustard, followed by intensive x-ray therapy for Hodgkin's disease involving the mediastinum and cervical nodes. There has been no evidence of recurrence to the present. This illustrates a response to the procedure, but an isolated result does not, of course, prove the additional value of nitrogen mustard.

The second and major indication for these agents is the symptomatic patients with Hodgkin's disease who have fever, itching, anorexia or weakness. In these patients excellent symptomatic relief may be obtained for long periods of time by the administration of suitable doses of nitrogen mustard or related compounds. Again, local radiotherapy, if the exact location of the disease is known, is preferable, but if it is hard to localize the disease, then a systemic medication is useful.

Figure 8 shows a patient who had extensive radiotherapy to the mediastinum for a number of years, but returned with cough and fever. Further x-ray treatment to the chest was considered to be hazardous because of the possibility of inducing pulmonary fibrosis. For a period of eight months this patient was maintained on oral TEM, and initially she showed an excellent response. However, she finally became resistant and died of disseminated disease.

The third indication is a situation in which local disease is threatening life, and a prompt therapeutic response is essential. Examples of these problems are: spinal cord compression with rapidly developing

Fig. 8.

evidence of paralysis; cardiac tamponade due to pericardial involvement; or compression of the trachea. In these situations we have given nitrogen mustard, 0.4 mg./kg. in single doses with prompt relief, in many cases, of symptoms and signs produced by the local disease. This treatment is followed immediately by intensive radiotherapy to the involved area in order to prolong the response. Thus we have a combination of immediate relief produced with less hazard than from the use of local radiotherapy, because x-rays may take several days to produce a response, and they are reputed at times to cause swelling of the tumor before it begins to regress, with a prolonged local effect resulting from local radiotherapy.

A fourth indication is in patients who have advanced Hodgkin's disease, who have had a maximum amount of x-ray therapy, and who seem refractory to any further treatment. In these situations we believe it essential that the patient receive an adequate trial of some type of alkylating compound. Occasionally one can obtain a very satisfactory and prolonged response, and in such cases, the patient can be continued on further maintenance courses of HN2 or chlorambucil or a further trial of local radiotherapy.

Finally, we have used nitrogen mustard occasionally as a diagnostic test. One patient I can cite will illustrate this point. This was a 17 year old boy who developed pleural effusion with parenchymal infiltration, a large liver and a temperature of 106° F. This boy had several lymph node biopsies which were inconclusive. He was treated with many different antibiotics without effect on his persistent fever. The pleural

effusion was aspirated for diagnostic purposes and was classified as Class IV Papanicolaou, strongly suggestive of lymphosarcoma. This boy was put on adrenal steroids without improvement. He was given streptomycin and isoniazid because of the possibility of tuberculosis, without any benefit. His deterioration was marked, and death appeared to be a definite probability within a few days. He was given, therefore, a therapeutic trial of TEM. Within 48 hours the fever began to decrease and all manifestations of disease cleared. This was more than three years ago, and he has shown no recurrence to date. We don't know the exact nature of this boy's illness. Rather than be inactive when things were going badly, and when trials of antibiotics and steroids failed, it was advisable to give him a trial of the polyfunctional alkylating agents.

In closing, I would say that these agents have an important role in the management of lymphomas, but I will certainly not argue with Dr. Friedman about the superiority of radiotherapy in the great majority of situations.

MODERATOR FORKNER: *Dr. Karnofsky, what are the disadvantages of using alkylating agents?*

DR. KARNOFSKY: If I answer that Dr. Gellhorn will have nothing to say!

MODERATOR FORKNER: We shall skip Dr. Gellhorn for the moment and call on Dr. Burchenal.

DR. JOSEPH H. BURCHENAL: Dr. Forkner has asked me to talk about the uses of the steroids in lymphomas. Generally speaking, I think that the steroids should be saved until after the radiation therapy and nitrogen mustard-type agents have had their chance. It is true that the steroids will have a definite effect in decreasing the size of the liver, of the spleen and of the tumor masses in lymphosarcoma, reticulum cell sarcoma, and in chronic lymphocytic leukemia. However, they do not do it any better than radiation or nitrogen mustard, and generally not as well. For some strange reason in chronic lymphocytic leukemia, as nodes shrink and liver and spleen become smaller under steroid therapy, the white count very often increases. It is almost as if one squeezed the nodes and forced the cells out into the peripheral blood. Eventually, after longer therapy with steroids, the white counts will often return to reasonable levels and sometimes to a normal level. It seems to me that the greatest use of steroids in the lymphomas is in combating the hemolytic component of the disease. This is particularly true in chronic

lymphocytic leukemia, perhaps somewhat less so in lymphosarcoma, reticulum cell sarcoma and in Hodgkin's disease. Thrombopenia also occasionally occurs in these diseases, unconnected with therapy. It can also be a toxic manifestation, particularly of mustard therapy, as Dr. Gellhorn will discuss. For the thrombopenia that is on an immunological basis, the steroids are quite useful. This is particularly important, because this is the type of situation that cannot be treated well by mustard therapy, although radiation will sometimes handle it.

I don't believe that the steroids play much of a role in Hodgkin's disease, as far as active therapy of the disease itself is concerned. They can be used as supportive therapy in the patient who is very sick with a high fever and almost terminal. They can be used to hold the line between courses of radiotherapy or mustard therapy, but they do not have much effect *per se* in the treatment of the disease, although they are useful whenever a hemolytic or thrombocytopenic state is present.

As to the compounds that can be used, one can use ACTH to stimulate the patient's own adrenals, either by intramuscular administration in the form of gel, or intravenously by constant intravenous drip. Ordinarily, however, ACTH therapy will not be necessary, and one can use oral medication, such as cortisone, prednisone, or decamethazone. In general, I think one would now use a prednisone type of agent, as it does not have the undesirable effect on electrolytes that one sees with cortisone. One can use prednisone, Medrol, triamcinolone or decamethazone. At the present time I don't believe that we have any indication that one is any better than another, but I do think that this general group is superior to cortisone, because of the lack of effect on electrolytes.

When one is trying to treat chronic lymphocytic leukemia, lymphosarcoma or reticulum cell sarcoma, and to decrease the size of a massive liver and spleen, then I think one needs to use what we consider standard doses, which would be something between 100 and 200 mg. a day of prednisone, obviously divided into q.6.h. dosage. Although I don't believe that it is often necessary, one can also use massive doses of prednisone up to a gram a day, but I see relatively little indication for that. In order to combat the hemolysis or the thrombopenic states, smaller doses oftentimes are quite adequate, and we have seen patients who have been handled quite well on 20 to 40 mg. of prednisone per day. Dr. Forkner mentioned one case he had seen that had continued for a

very long period of time. I might mention a case that had been referred to me by Dr. Weisberger, in which death may possibly be attributed to the patient's having stopped taking his steroids. This man was president of a company, a very active man. At 72 years of age, he came to New York on a little holiday and stopped taking the steroids on which he had been maintained for some time because of difficulty with purpura. When he stopped the steroids, the purpura became much worse and he seems to have died of a cerebrovascular accident, in the 38th year of the disease. He was a fully useful member of society until a day or two before his death, a case that shows that chronic lymphocytic leukemia occasionally can be a very long drawn out disease and one that does not necessarily reduce the normal life span. This patient's long course was probably attributable to the nature of his disease, to the fact that he was aggressively treated with radiotherapy whenever necessary, and only in the latter stage of the disease with steroids. Dr. Gellhorn will discuss the various undesirable side effects of these steroids.

To sum up, I feel that the steroids should be saved for the very special situations, primarily the hemolytic and thrombopenic aspects of these diseases, and should be used only after radiation therapy and mustard therapy have been given their chance.

MODERATOR FORKNER: Dr. Gellhorn!

DR. ALFRED GELLHORN: We have heard about the management of this group of patients, and all of us in this room have had and will continue to have the opportunity and responsibility of treating these diseases. This is difficult, as we all know, because of their chronicity and the multiple problems which arise. We have heard indications for drug use, we have heard results that can be anticipated, and now it is only necessary to review together some of the things which we must keep in mind in the proper use of these agents; namely, the side effects that can come from the agents alone and that can come from the agents in conjunction with the natural history of the disease.

Let us start, because it was started thus on the panel, with a discussion of some of the side effects to be kept in mind when we refer our patient for radiotherapy. When the disease is localized and aggressive therapy is given, there are usually no significant complications that we, as referring physicians, will contend with, except that the patients may call us and tell us that the x-ray man has given them a terrible burn. Those of us who are not in radiology have a real responsibility to make

clear to the patient this statement about radiation burns, because it is loosely used by patients. Either by concurring, because it is the easy way, or not making comment, physicians frequently seem to give tacit agreement. We should explain that the skin erythema is an expected reaction and will subside. When localized disease is present in the supraclavicular areas, and heavy radiation is to be given to this area, it is important to know that there is not an underlying acid-fast lesion present. Irradiation in this situation can lead to miliary dissemination of tuberculosis. An appropriate anti-tuberculosis prophylactic chemotherapeutic regimen should be instituted before initiating radiotherapy. When Dr. Friedman indicates he has tried aggressive radiotherapy to multiple sites, then we may encounter some other complications. Thus, if radiotherapy is used in multiple areas, there may well be a depression of bone marrow similar to that observed with alkylating agents, with all the attendant problems that arise from such an effect. In addition, if irradiation is given to mediastinal structures, and possibly repeatedly, problems of fibrous tissue reaction in the irradiated tissue may occur and the patient may ultimately have impaired respiration due to pulmonary fibrosis.

Turning now to chemotherapeutic agents, the list of side reactions and complications is considerable. On the other hand, if we recognize them and know the mechanisms that are behind them, these agents, as has been indicated by Drs. Karnofsky and Burchenal, are tremendously valuable in our management of patients with lymphomas.

(Slide) In the case of the alkylating agents, as Dr. Karnofsky has indicated, the drug most frequently used, even nowadays, is nitrogen mustard given intravenously. This has two major effects. One is on the central nervous system, an immediate toxic effect, and it is manifested by stimulation of the vomiting center, producing the nausea and vomiting with which we are all familiar. At the present time, with the drugs available for combating such a reaction from the stimulation of the vomiting center, this type of side effect can be markedly minimized. The other important effect of nitrogen mustard is on bone marrow functions. As you know, the effect is not immediately apparent, but there is a delay, and usually the peak effect, as manifested by changes in peripheral blood, can be seen within 7 to 15 days following the completion of a standard course of nitrogen mustard given intravenously. There are several things which I think are worth re-emphasizing. Al-

though there is a pancytopenia in many instances, the leukopenia is characterized not by agranulocytosis, but by lymphocytopenia. Although the total count may be reduced, the proportion of neutrophils present remains high and therefore the frequency of infections is not as high as one would anticipate. Severe thrombocytopenia does not usually occur the first time that the patient is given a chemotherapeutic agent; but in patients who have had previous treatment, thrombocytopenic bleeding may be an important complication. Dr. Burchenal has indicated one of the means of attempting to modify this particular reaction.

The anemia that does occur is one that is usually self-correctable if a remission is produced in the disease.

With regard to other alkylating agents, triethylene melamine (TEM), TEPA, chlorambucil, uracil mustard, which is really just another nitrogen mustard, the side effects are qualitatively similar to those of nitrogen mustard. Usually, the stimulation of the vomiting center is less with the majority of these and therefore nausea and vomiting are not prominent symptoms. Marrow depression also occurs, but because these other agents have a variable rate of absorption from the gastrointestinal tract when given by mouth, or have a more delayed onset of effect when given parenterally as in the case of Thio-TEPA, they are less predictable, in terms of marrow depression, than nitrogen mustard. This is important for us to bear in mind if we plan to use these agents, for we should not necessarily anticipate that our peak depression in blood count will appear at the end of two weeks. Rather, we should keep observing patients over a period of three weeks, or even more, before going on with higher doses than those recommended.

(Slide) There are, in addition, certain complications that occur with alkylating agents that it would be well to mention, particularly in patients with lymphomas. These have to do with infection, not necessarily because of leukopenia, but when the leukopenia is combined with a depression of the normal gamma globulin, a phenomenon which occurs in approximately 30 per cent of the patients with lymphosarcoma and chronic lymphatic leukemia. It has been observed in a group of patients studied at our institution that, with hypogammaglobulinemia, infections not only occur with greater frequency in these patients than in those with lymphoma and no hypogammaglobulinemia, but the morbidity is considerably greater.

Also, since these agents may have a dramatic effect on a tumor when given, there may be a rapid dissolution of tumor and the blood uric acid may become markedly elevated, leading to renal complications. One must therefore bear in mind that hyperuricemia is possible, know about it beforehand and take appropriate measures, such as adequate hydration, to prevent its leading to significant damage of renal function.

On rare occasions, following the administration of nitrogen mustard, dissemination of miliary acid-fast infection may occur. It is well to keep this in mind. Know your patient in order to be forewarned and prevent such a possibility.

Turning to the steroids which Dr. Burchenal has presented, we shall review the side effects known to all of us. These include the Cushing facies, the important problem of gastrointestinal ulceration and therefore the necessity, when our patients are put on dosages such as Dr. Burchenal suggests of 100 mg. of prednisone, of placing the patient on a well-planned and specific ulcer regimen. The psychic effects of these steroids are important. We hope that the patients will have a euphoric reaction, but many of them become paranoid, and this effect must be looked for in our contacts with the patient in order to prevent disastrous results. Electrolyte changes can occur with these agents. Again, even though the compounds mentioned by Dr. Burchenal cause less sodium retention than cortisone, nevertheless, in the doses that we employ, there may be sodium retention with the associated edema; there may also be loss of potassium and attendant manifestations of asthenia from hypokalemia. Therefore, when patients are put on large doses, additional potassium chloride is given. Patients should be examined before being put on steroids, to determine whether they have any evidence of diabetes, for there will certainly be increased hyperglycemia, glycosuria, and the hazard of diabetic acidosis.

It is also well to bear in mind that patients on any of these doses of steroids over prolonged periods of time have a greater susceptibility and frequency of infection with saprophytic organisms such as with monilia. This not only presents local problems in the buccal cavity, but can produce systemic infection. The fungi are important, in terms of their systemic infection of the lungs or, perhaps even more important, involvement of the central nervous system, as by cryptococci. Other infections also have an opportunity for dissemination, pyogenic and tuberculous being the ones that should be borne in mind.

Finally, we must be aware that, if our patients are to be placed on these agents for control of hemolytic activity for a considerable period of time, there will be a depression of osteoid deposits. The x-ray will demonstrate progressive osteoporosis; and it can be anticipated that a significant number of our patients will develop compression fractures with the symptoms attendant thereon. These, then, are some of the side reactions. It seems to me that none of them constitutes such overwhelming contraindications that we would not consider the use of either irradiation or the chemotherapeutic agents, but certainly we must know them in order to manage our patient well and totally.

MODERATOR FORKNER: I gather, Dr. Gellhorn, that you are not quite in agreement with Dr. Friedman about aggressive treatment. My feeling has always been that, with this group of incurable patients, all one can hope to do is to improve them symptomatically and to prolong their useful lives. In my experience, the minimum amount of x-ray therapy which can relieve the symptoms is the desirable amount, rather than the administration of the maximum amount which one can deliver to any one particular area. *May we have some discussion on this subject, Dr. Friedman?*

DR. FRIEDMAN: What I mean by aggressive treatment is that dose of radiation, delivered to the diseased nodes, and to other lymph node regions prophylactically, which will prevent a recurrence of the disease in the irradiated area throughout the rest of the patient's life, with the exception of the 10 per cent of cases in whom the recurrence appears in the terminal phase of the disease. If one gives minimal doses of irradiation, they must frequently be repeated one or more times, so that the total dose delivered to each area is ultimately larger than that of a single course of the so-called aggressive irradiation that I give; and the incidence of radiation ulcers is much higher. Finally, the survival rates following the small-dose techniques are much lower than the survival rates following aggressive irradiation.

DR. GELLHORN: I would like to rise to this one. I don't believe that any person interested in chemotherapy at the present time would suggest the use of these agents in the management of disease which is clinically localized, and I believe that most of us feel that, when on clinical examination the disease is found to be limited to one site or to one region, the treatment of choice is x-ray therapy. Unlike Dr. Forkner, we believe, under these circumstances, that a tumoricidal dose should be

given. However, I think we would take real exception to Dr. Friedman's plan in an individual who has clinically evident disease in multiple sites. On the basis of what most of us observe in the natural history of the disease, the process is not limited to just those areas that we can recognize clinically but is certainly also present elsewhere. Recognizing that the human organism can tolerate only so much radiation, it seems to us unwise to deliver such tumoricidal doses to multiple sites of the body.

DR. BURCHENAL: I would like to ask Dr. Friedman a question.

DR. FRIEDMAN: May I first briefly answer Dr. Gellhorn's statement concerning the aggressive irradiation technique for widespread disease. I showed six examples of patients with widespread disease who had survived for five years, and in Table III a 32 per cent five-year survival rate for 150 patients with Stage III Hodgkin's disease. Now, Dr. Gellhorn, I think you have published some rather favorable figures. Were they comparable with mine?

DR. GELLHORN: No, no, these patients received irradiation *and* chemotherapy. When the disease was disseminated the patient received chemotherapy if the manifestations were constitutional in nature, and received irradiation for problems of pressure in various areas when this was indicated.

MODERATOR FORKNER: Dr. Burchenal!

DR. BURCHENAL: I wanted to ask Dr. Friedman if he has ever tried this. I believe it is known that in animals, if small areas of the body are irradiated, one at a time, larger doses can be given. I wonder if he has ever tried giving aggressive radiotherapy to Hodgkin's disease, taking segments of the body; for example, the lower quarter, the in-between quarters, and so on, with the idea that if one can prevent recurrence from one area one might, by covering the whole body over a given period of time, not wipe out the bone marrow, give it a chance to recover, and still prevent the Hodgkin's disease from recurring?

DR. FRIEDMAN: I have not tried it because others have tried it, with results that I anticipated; namely, with doses much lower than that required to destroy Hodgkin's disease, there was a profound depression of the bone marrow.

DR. BURCHENAL: Do you think the bone marrow in a given area would recover at all after 2000 r—if you gave a segment, say this wide (indicating), would the bone marrow in the ribs recover, if two weeks

later you were treating another segment, and later on another?

DR. FRIEDMAN: If one undertook to give 2000 r to the whole body, one would kill most of these patients. The bone marrow in each irradiated area would not recover in the period that you specify.

DR. BURCHENAL: If one took a year to do it, the patients ought to be repopulating their blood from normal bone marrow.

DR. FRIEDMAN: If one gave it over a period of a year, the marrow in many patients might recover but there would be a significant number of deaths, enough to discourage further use of the technique. I don't think radiation cures the disease. In our Walter Reed series there were about eight patients who died, and at postmortem examination there were no manifestations of the disease.

MODERATOR FORKNER: There are a number of questions from the floor. The first is referred to Dr. Karnofsky. "*A white male, age 28, for one year has had substernal discomfort, two episodes of fever unresponsive to antibiotics. X-rays of the chest show a progressively enlarging mediastinal mass and abdominal films show enlargement of the spleen, which is not clinically palpable. Routine blood counts and bone marrow aspiration biopsy were unrevealing except for slight anemia. No lymph nodes were enlarged. What is the next step? Should one explore the mediastinum for a biopsy, or should one be satisfied with watchful waiting?*" *Dr. Karnofsky, can you answer that very briefly?*

DR. KARNOFSKY: I think I can answer the question academically, although one does not always practice what one preaches. Before treating a lymphoma, except in the most remarkable circumstances, one should first make sure of the diagnosis. I realize that strenuous efforts have been made to establish a diagnosis in this case. I certainly think one should seriously consider a thoracotomy in this patient. The morbidity and mortality from that procedure are low, and it would be far more important to know whether this patient has lymphoma and treat him adequately than to forego the hazards of the thoracotomy and treat him empirically and not know what is going on until perhaps very late in the disease.

MODERATOR FORKNER: Dr. Friedman, here is a question that belongs to you. "*In view of the leukemogenic effects of radiation, are you not afraid of converting lymphoma into frank leukemia?*"

DR. FRIEDMAN: The detrimental effects of radiation have been wildly exaggerated. In general, when one is treating a patient for a specific dis-

ease, the question of leukemogenesis by radiation does not enter; the problem of leukemogenesis induced by radiation arises only when the individual being irradiated is either normal, or when one is considering extensive radiation for a very benign disease such as arthritis of the spine.

MODERATOR FORKNER: This physician asks, "*What are the comparative results of no therapy in Hodgkin's disease with radiation therapy?*"

DR. FRIEDMAN: I don't think there is a valid, comparable series of patients with Hodgkin's disease not having been irradiated. However, there is no question that in Hodgkin's disease, treated either with radiation or alkylating agents, the survival rates are much greater than without treatment. I refer you to Table IV which shows a marked increase in survival rates with modern aggressive treatment techniques.

MODERATOR FORKNER: Also, patients are made much more comfortable while they do live.

Dr. Gellhorn, will you discuss the management of the patient with intractable generalized pruritus as a result of Hodgkin's disease?

DR. GELLHORN: This is one of the very good indications for the use of nitrogen mustard, and usually an effect can be anticipated in a short period of time, with relief of distressing symptoms. The alternative is treatment of the patient with x-ray. Usually, in this instance, the treatment consists of radiation to the retroperitoneal area. This is also effective, but the onset of benefit is usually more delayed than that following intravenous administration of an alkylating agent.

MODERATOR FORKNER: *What are the effects of steroids in such cases?*

DR. GELLHORN: Steroids in such instances would also be expected to have a beneficial effect on pruritus. The reason that I would not recommend such therapy is that, once started, it is necessary to continue with the steroid, for when the steroid is discontinued the pruritus and other manifestations will promptly recur.

MODERATOR FORKNER: The next question is addressed to Dr. Friedman: "*Under what circumstances do you irradiate the liver, without irradiating the remainder of the abdomen?*"

DR. FRIEDMAN: When the liver is enlarged with disease, and the patient is not in a truly terminal phase of disease, it is a simple matter to irradiate the entire liver with large tumor doses, up to 3500 r. There is minimal or almost no radiation sickness. We use it commonly when carcinoma of the breast has metastasized predominantly to the liver. However, in lymphoma the liver becomes enlarged in the terminal phase

of the disease when one is dealing with a sick patient with anemia and general effects of the disease; under these circumstances, irradiation becomes less effective than in a healthy patient.

MODERATOR FORKNER: *Dr. Karnofsky?*

DR. KARNOFSKY: I would be a little more optimistic about liver irradiation. When the liver becomes enlarged I don't think it necessarily represents a terminal phase of the disease any more than any other generalized manifestation of the disease, and, even when alkylating compounds have not produced a satisfactory systemic response, and the liver remains enlarged, local radiotherapy of the liver has often been effective.

MODERATOR FORKNER: *Dr. Burchenal, is it true that chlorambucil is more effective against lymphocytes than against the remaining blood elements?*

DR. BURCHENAL: I think that chlorambucil, along with other nitrogen mustards, the bis beta chlorethyl compounds, do have a slightly greater effect on the lymphocytes. On the other hand, if enough is given, it will depress everything. This compound was first tested by a group at the Chester Beatty Institute. They felt that Myleran was specific for granulocytic leukemia, whereas chlorambucil was specific for lymphocytic leukemia. I don't think it is quite as black and white as that would indicate. Certainly Drs. Karnofsky, Sykes and Krakoff have shown that chlorambucil will act against chronic granulocytic leukemia and Myleran will act against some of the chronic lymphocytic leukemias.

DOCTOR: *Would radiotherapy to a massively enlarged spleen be of use in chronic myelogenous leukemia with falling hemoglobin, normal white blood cell count and normal platelets?*

MODERATOR FORKNER: The answer is yes. Any objections?

Patients with lymphoblastoma often are given large doses of vitamins by their physicians because they are ill. What do you think of that, Dr. Gellhorn?

DR. GELLHORN: I think it is fine for the vitamin manufacturers, but I don't think it does any good to the patient.

MODERATOR FORKNER: *Do you think it might do harm?*

DR. GELLHORN: Well, I suppose that if one gives enough A or enough D, one can conceivably get into problems, particularly disturbances of calcium metabolism.

MODERATOR FORKNER: *What about folic acid?*

DR. GELLHORN: I think that the rate of excretion of folic acid would probably be able to keep up with most administration, so that the vitamin does neither good nor harm.

MODERATOR FORKNER: *Dr. Burchenal, are the antifolic acid compounds of any use in this group of diseases?*

DR. BURCHENAL: In lymphosarcoma of childhood, the antifolics may occasionally work reasonably well. In lymphomas in general, they have no place. In chronic lymphocytic leukemia, or in the lymphosarcomas in adults that we have seen, they do nothing.

MODERATOR FORKNER: There is another point that I would like to bring out. If the panel disagrees with me I would like to have them say so. Patients with these diseases should not be treated simply because they have the disease. I have seen many patients in whom I have delayed treatment for months and years simply because they had no significant symptoms of the disease. They were not losing weight, had no anemia, they had no fever, no pruritus, but they did have one of these diseases. Making the diagnosis is not an indication for treatment. One should delay treatment until one gets some indication that the disease is progressive and is producing symptoms. *Is there any disagreement?*

DR. GELLHORN: I would like to make a qualification. I subscribe to that except in patients who have localized disease. In such patients, who may be asymptomatic, it is important to provide treatment for them.

DR. BURCHENAL: I would agree on not treating asymptomatic chronic lymphocycotic leukemia, but I would like to see a localized lymphoma treated aggressively immediately after the diagnosis is made, with the hope of eradicating it.

MODERATOR FORKNER: *Have you ever seen these diseases eradicated by such aggressive measures?*

DR. BURCHENAL: We have had patients with no evidence of disease for five, ten or more years. Whether or not the disease will eventually recur we cannot say.

MODERATOR FORKNER: It seems to me that if one could find a local, accessible group of nodes in Hodgkin's disease, it might be wise to extirpate the nodes with surgery and then treat with x-rays. *What is your view on that?*

DR. FRIEDMAN: There are several reports, including one by Sugarbaker, showing gratifying five-year survival rates from surgical block dissection of the regional group of nodes with Hodgkin's disease. How-

ever, most of his patients had postoperative x-ray therapy. Although block dissection and resection of a localized group of nodes is efficient, I see no reason for radical surgery, when irradiation is so much easier. Furthermore, most of the surgery patients need irradiation to other areas later on to permit them to survive five years.

DR. BURCHENAL: Would you be willing to do just surgery? Would you not want to irradiate the adjoining nodes as well?

DR. FRIEDMAN: I would prefer to use radiation initially.

DR. BURCHENAL: We would not mind using surgery if the disease were localized.

MODERATOR FORKNER: *Are there any other points the panel would like to bring out?*

DR. KARNOFSKY: That we should not do anything in the asymptomatic patient is, I think, an oversimplification. In patients with localized disease present in an area where it can produce serious complications, I think it is worth treating, rather than waiting until the patient begins to complain of symptoms.

MODERATOR FORKNER: One should watch his patients carefully in order to anticipate symptoms.

DR. KARNOFSKY: When does one start treatment? If one waits passively until the disease does something which produces symptoms, I presume you would start treating then?

MODERATOR FORKNER: The symptoms may include a loss of five or ten pounds body weight, there may be a little anemia; the patient himself may not complain, but if you watch him carefully and observe the usual features, one can almost invariably predict when these patients are going into relapse.

DR. KARNOFSKY: You are talking about doctors who spend their lives studying the disease. In general practice, apathy in management is not the same thing as the specialist predicting and anticipating and waiting until the proper stage of the disease is reached before treatment is started. I think one sometimes has to treat if a patient has no symptoms of the disease, because the disease is present in a strategic area and it may enlarge at a subsequent time to produce trouble.

MODERATOR FORKNER: In this disease, as in other diseases, one of our chief faults is overtreating the patient.

Thank you all very much.

The Fenwick Beekman Collection*

An institutional library, no matter how old or large, is immeasurably enhanced by the gift of the library of a collector. Library funds, even when supplemented by the generosity of a "Friends" organization, do not permit the librarian the luxury of devoting all resources to the contributions and life of one man or one phase of a subject. The collector can give his time, attention and affection to his pursuit. The librarian must consider a larger horizon with much less concentration. So the last year has indeed been a memorable one for the Academy Library, which received the deed of gift of Dr. Robert Levy's incomparable Harvey collection, the charming prints and woodcuts from Dr. Hayes Martin and Dr. Beekman's splendid library.

The Beekman collection of John Hunter has been called the finest one in private hands. Now added to the holdings of the Academy it may be considered second only to that in the Royal College of Surgeons. The many editions of John Hunter's works, the lecture notes taken by his students, the volumes of the *London Medical Journal* and the *Medical and Philosophical Commentaries*, the Hunterian orations and transactions, are the substance one would expect to find. Beyond these is the importance of bringing together the mass of memorabilia, of unusual small pieces, of the writings of his contemporaries, of later historians, which supplement or comment upon his achievements. Together they illumine the man, his era and the history of surgery.

Original letters of course are a highlight of such a library, and Dr. Beekman has three of John Hunter's with photostats of others and with original letters of some of his colleagues. In one volume, an extra-illustrated copy of Ottley's *Life of John Hunter* are many pictures, letters, clippings, gathered by another devotee and preserved for future enthusiasts. Seven stout folios contain pamphlets garnered by Sir D'Arcy Power; eight others of the same sort were bound by Dr. Beekman. One small volume, acquired after twenty years of search is a fantasy called, *Only an Old Chair*, Edinburgh, 1884. It tells the tale of a chair in the Hunter home and the distinguished personages who sat in

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Courtesy of the N. Y. Historical Society, New York City

FENWICK BEEKMAN, M.D.

it. The chair itself was of interest, one of a set made from wood brought from the South Seas by Capt. Cook. There are other mementos "from the cradle to the grave." Here is a charming water color by Dr. Beekman of Long Calderwood, Hunter's birthplace, to which Dr. Beekman made pilgrimage. There is the rubbing made from his coffin plate in the vault of St. Martins-in-the-Fields church in 1859; an announcement of the sale of his estate in 1794; a photostat of pages in the *Illustrated News of the World*, April 2, 1859, showing the discovery of his remains and their reinterment in Westminster Abbey. There are pictures, too, of the Hunters and their friends, of St. Bartholomew's Hospital, St. Thomas's Hospital, a ward in Middlesex Hospital. These and many more await the historian seeking small details, obscure facts and illustrations.

Although John Hunter is the hero of the collection, the leading man, other stars are included in a separate section, not concerned with Hunter and his times. There are first editions of Jenner and Beaumont, of Cowper's *Myotomia reformata*, 1694, Cheselden's *Osteographia*, 1733, Bidloo's *Anatomia*, 1685, two copies of Wiseman's *Severall chirurgicall Treatises*, 1676, one a superb large clean copy, and the English Paré of 1634. There is the small Harvey, *Anatomical Exercitations*, 1653, and the very big Astley Paston Cooper, on hernia, 1804. Sir Thomas Browne is represented by his *Works* of 1686, and all of the editions of MacMichael's *Gold-headed Cane* may be found, one a most interesting extra-illustrated copy of the 1923 edition. Mention must be made, too, of the many histories, biographies and bibliographies which round out this valuable group. Space forbids elaboration upon three other subjects unusually well covered: anesthesia, Darwin, and the Resurrectionists. The latter, in particular, has many most unusual and fascinating items. One volume alone is a major contribution to the literature, for it has bound together many pamphlets, broadsides, illustrations, even an autograph letter of the infamous William Burke. Among the Darwin books is the 1859 *Origin of Species*, and the 1872 *Expression of the Emotions in Man and Animals*, which is inscribed by the author.

Obviously, many are duplicates of works already on our shelves. Fortunately, a large number provide us with better copies of old volumes or fresher copies of much used reference tools. The Hunterian part of the collection will be preserved as a unit, and no duplicates will be removed. Unwanted duplicates of the remainder of the collection, however, will be passed on to

libraries not in the metropolitan area. Twelve volumes have already been sent to the Upgraded Department of the History of Medicine, Osmania Medical College, Hyderabad, where efforts are being made to build a useful library on the history of medicine in an area previously without one. Others will be sent to the fledgling library at the University of Miami School of Medicine, Jackson Memorial Library.

We cannot end this brief glance at Dr. Beekman's "children" without a reference to his bindings. When he retired after a distinguished career as a surgeon, Dr. Beekman was not content to sit idle. He went to the studio of a master craftsman to learn hand bookbinding. The skillful results of his labors are plain to see, and will well cover and preserve some of his cherished texts for the future. The Library is surely enriched by this munificent gift.

GERTRUDE L. ANNAN, *Librarian*

John Hunter's Contribution to Pathology*

PAUL KLEMPERER**

Consulting Pathologist, The Mount Sinai Hospital, New York

Sir James Paget in his Hunterian Oration of 1877, asserts that, "among the pathologists of his time he was by far the first." What was the state of pathology in the second part of the eighteenth century? Hieronymus D. Gaub, Boerhaave's successor in Leyden published in 1758 the first edition of *Institutiones Pathologiae Medicinalis* which for more than a generation was regarded as the most comprehensive treatise on "*Pathology*, which is the theory of the diseased state." He called pathology "whatever ought to be known with regard to the nature, causes and seats of diseases." This seems to be an adequate definition; but the book in sum and substance is a medley of the ancient Methodists' principles of the status strictus and laxus dependent on the pore size of the solid parts and humoral pathologic ideas interpreted by iatromechanical as well as iatrochemical doctrines. The absence of any sound foundation for his concept of pathology becomes evident in his paragraphs on the diseases of the solid parts of the human body where one misses any reference to morbid anatomy which by that time had already made important contributions to the comprehension of disease symptoms in terms of anatomic organ alterations. Gaub's book reflects an almost hopeless state of general pathology. While one hopefully reads the assertion in the author's preface "that everything taught in Pathology ought to be of some use in the practice of physic" one agrees, after perusal of the book, with the subsequent statement in the preface that "I am in doubt whether mankind are more benefited or hurt by the medical art." It is in comparison with this low level of general pathology that one has to appraise the contribution of John Hunter to its progress. It is true that only three years after the publication of Gaub's book Morgagni issued his immortal treatise, *On the seats and causes of diseases investigated by Anatomy*. Retrospectively, we know that this work became the foundation of the development of modern general pathology but at the time of its appearance it

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** The author is greatly indebted to Dr. Fenwick Beekman's magnificent collection.

did not reveal all the opportunities which a rational correlation of bedside symptoms with autopsy observations can provide for the comprehension of the causes of disease. Morgagni limited his investigations and conclusions to the demonstration of the correspondence of morbid symptoms with organ alterations. He kept aloof from speculations as to the remote causes of disease and concerned himself only with the proximate reasons which he saw in the anatomical organ changes.

By virtue of his fundamental training and research in anatomy it is conceivable that Hunter originally adopted a similar philosophy in his investigations of human disease. This assumption is supported by the lines of Benjamin Alexander, who dedicated the third volume of his translation of Morgagni to him: "For myself I must confess, that it is to you, chiefly, I owe that little share of anatomical science, of which I am possessed. From thence arises every degree of certainty that I find in determining the seats and in great measure the causes of diseases. And though I do not affect to despise, but even greatly esteem the science of Chemistry and other branches of Natural Knowledge, auxiliary to Medicine, I cannot, however, but give the first place to Anatomy, as being the very basis, the groundwork and indeed, as I may be allowed to speak thus, the grand luminary of physik." The supposition that Hunter favored Morgagni's aim of correlating clinical symptoms with anatomic observation is further supported by Alexander's reference, "great as I have frequently known you confess him." This position as morbid anatomist is revealed by his description and discussion of two cases of cardiac anomaly, one of a long standing aortic insufficiency, the other of a ventricular septum defect. Here he explains in detail the abnormal cardiac action, evidenced by the clinical symptoms with reference to the anatomical situation. His appreciation of morbid anatomy as a key to the comprehension of clinical symptoms is frequently illustrated by the detailed clinical abstracts accompanying the pathologic specimens of his museum. Yet, he did not limit his inquiry to the seats and proximate causes of diseases but extended its scope to a search for the hidden causes and the mechanisms by which they act. The morphologic alteration of organs was for him the *product* of disease and the disclosure of the *morbid process* the aim of his investigations. He was convinced that knowledge of pathogenesis was the foundation for an understanding and ultimate alleviation of disease. But he was not satisfied with vague concepts and speculations to explain away the morbid events such as had been proposed by pathologists like Gaub. "In Natural History we are

often made acquainted with the facts, yet do not know the cause. Therefore, we are obliged to have recourse to experiments to ascertain the causes which connect the facts, one leading into the other, making a perfect whole; for without the knowledge of the causes and effects conjointly, our knowledge is imperfect." This is the rationale of Hunter, the experimental pathologist. It can be affirmed that his dynamic concept ushered in a new era of pathology. The collection of Hunterian orations bears witness to the undiminished appreciation of his contribution over a century and a half.

The preceding remarks must not be understood to imply that the basic concept of pathogenesis originated with Hunter. The question as to the origin of disease is ancient. Hippocrates and Galen found it in a faulty mixture of the humours, the Methodists in an alteration of the pore size of the solid components of the human body. With the rise of morbid anatomy alterations of organs were regarded as the proximate cause of disease; but it was obvious that the abnormality of structure demanded further explanation and both iatromechanical and iatrochemical doctrine attempted to account for it. John Hunter was the first who recognized the impasse of speculative medicine and tried to ascertain the genesis of morbid lesions by exact observation and appropriate experimentation. By placing the pathogenetic principle above mere description and classification according to topography (a capite ad calcem) Hunter advanced beyond the scope of Morgagni and gave, as Hodgson said, "to Pathology the character of rational science and a place in true Philosophy." Because of his distrust of "the prepossessions of chemical and mechanical philosophy" in the considerations of "the actions and production of actions both in vegetable and animal bodies," he based the interpretation of his biologic observations on the assumption of a specific vital force.* This concept is today no longer acceptable. But for nearly a century it dominated the theory of pathology, although the exclusive formulation of Hunter and subsequently of Bichat met increasing opposition. The advances of the basic sciences during the nineteenth century led to its gradual reversal and final defeat in our times.

Hunter did not publish in a treatise his morbid anatomic observations but his collection of and notes on pathological specimens testify to his endeavor to classify morbid lesions according to pathogenetic principles.

*For a condensed view of Hunter's idea, see James F. Palmer's footnote, Vol. III, of the works of Hunter, pages 120, ff.

His nephew and disciple, Matthew Baillie, codified the master's ideas in the first systematic textbook of morbid anatomy in 1793. *The Descriptive catalogue of the pathological specimens contained in the museum of the Royal College of Surgeons of England* was completed by E. Stanley and J. Paget in 1846 following Hunter's plan and is a brilliant outline of a general and special pathologic anatomy as it was conceived by John Hunter. Pathology of today has far advanced beyond the scope of the 18th and 19th centuries but John Hunter must always be gratefully remembered as one of its important architects.

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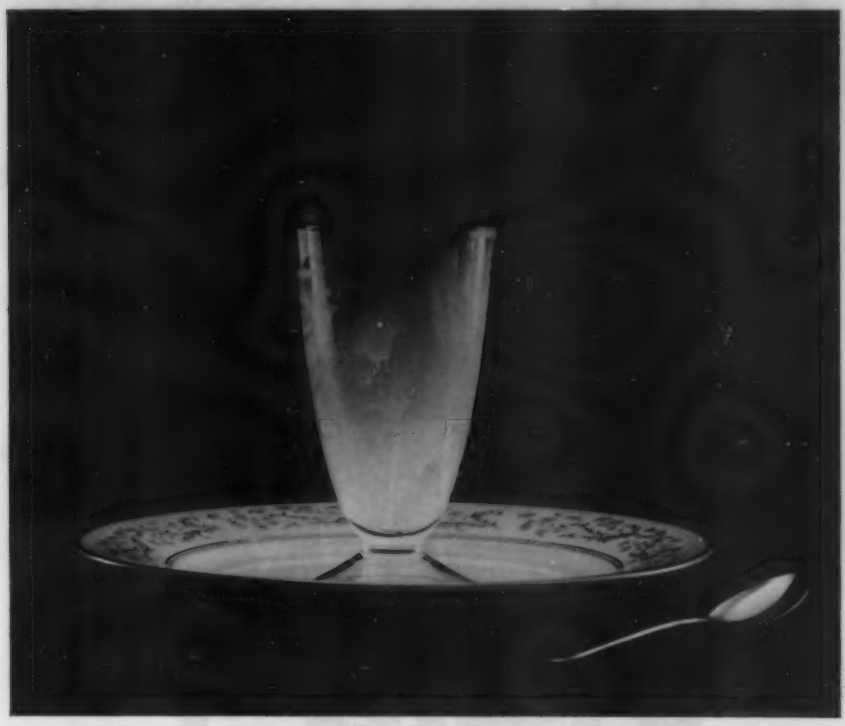

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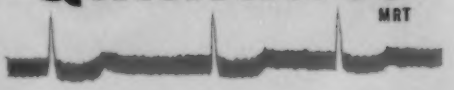

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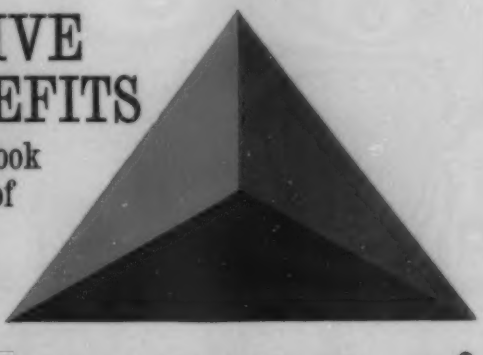

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'MIGRAL' permits maximum ergotamine therapy with the first dose —because the 'MIGRAL' formula includes the proved antiemetic, cyclizine hydrochloride, to counteract the tendency to nausea and vomiting.

Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.

Each sugar-coated 'MIGRAL' tablet provides:

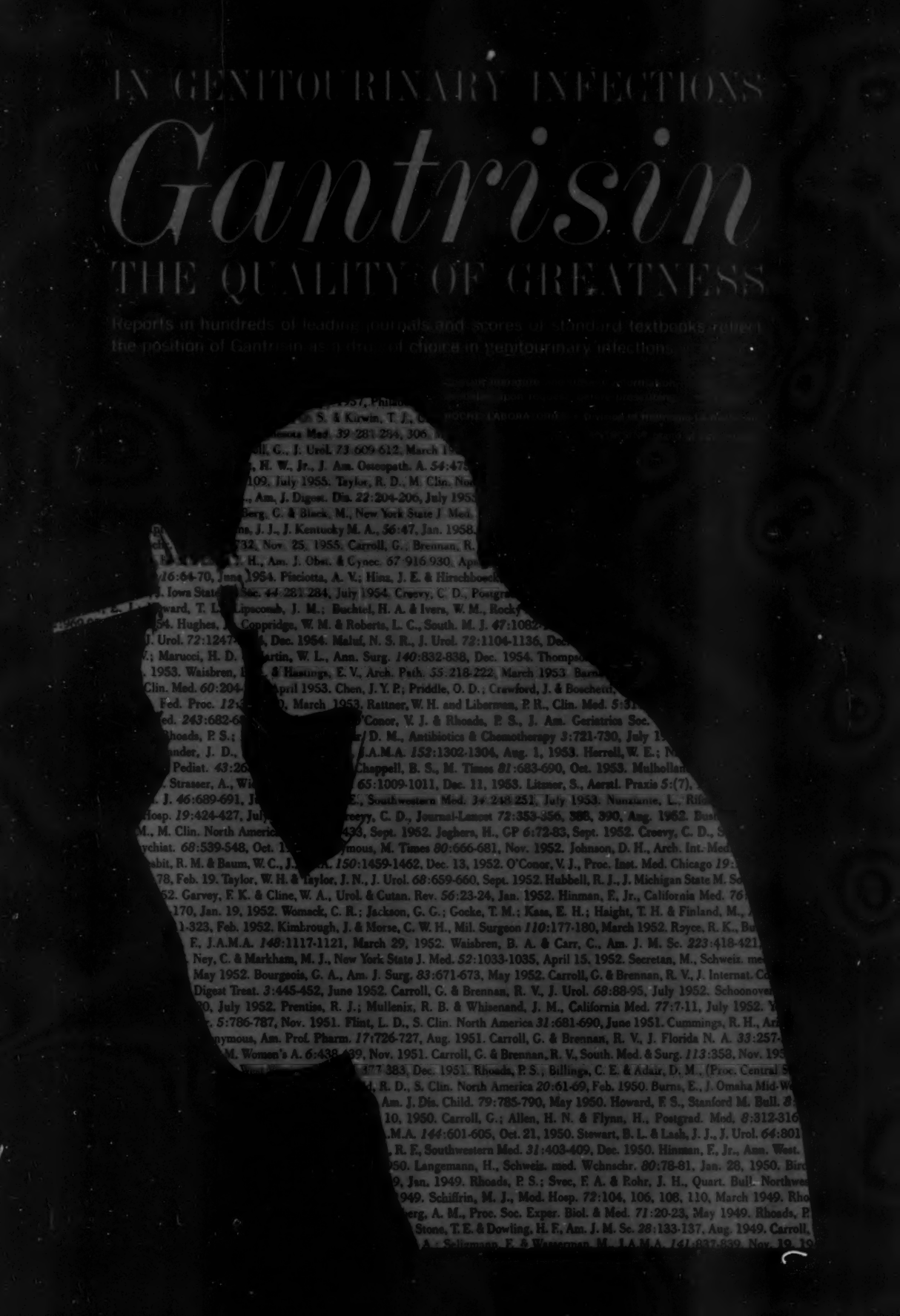
Ergotamine Tartrate	1 mg.
'Marezine'® brand Cyclizine Hydrochloride	25 mg.
Caffeine	50 mg.

In bottles of 20 and 100 tablets.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

IN GENITOURINARY INFECTIONS

Gantrisin

THE QUALITY OF GREATNESS

Reports in hundreds of leading journals and scores of standard textbooks reflect the position of Gantrisin as a drug of choice in genitourinary infections.